A Theoretical and Experimental Investigation of Stereoselective Iodolactonisation

Stewart Bissmire

Thesis Submitted for the Degree of Doctor of Philosophy at Cardiff University

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789 East Eisenhower Parkway
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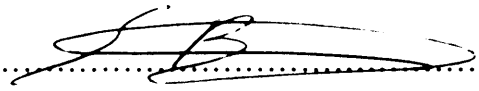
Signed  .....(Stewart Bissmire)

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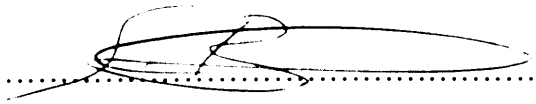
Signed  .....(Stewart Bissmire)

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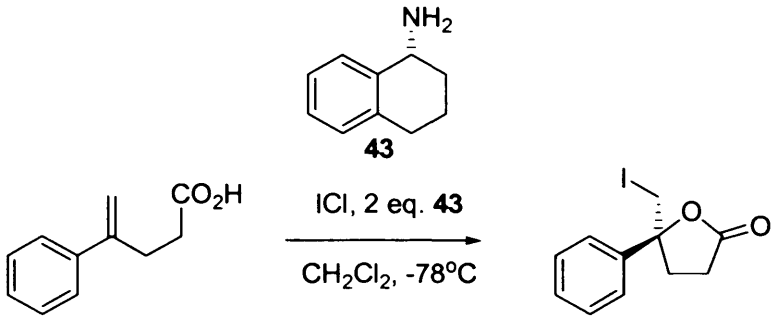
Abstract

Lactonizations are important steps in many synthetic sequences. Substrate-controlled reactions that use chiral auxiliaries or chiral alkenes have already been studied in depth. This study focuses on stereoselective reagent-controlled iodolactonizations, by application of a new method that uses complexes of iodine monochloride and various donor molecules. (*R*)-1,2,3,4-Tetrahydro-1-naphthylamine and other amines with similar structures were synthesized and found to be efficient in the iodocyclization of 4-aryl-4-pentenoic acids and other similar substrates. Calculations were performed on complexes of (*R*)-1,2,3,4-tetrahydro-1-naphthylamine with XCl (X=I, H) to identify possible reactive species in these iodocyclizations. Various levels of theory were employed, including B3LYP/6-31+G (d,p) using a modified SDD basis set for iodine.

Summary

Lactones are important substructures in many natural and pharmaceutical products. Substrate-controlled reactions, where a present chiral centre within the substrate dictates the chirality of a new centre formed during a reaction, have already been studied in depth. This study focuses on the stereoselective reagent-controlled iodolactonizations of of 4-aryl-4-pentenoic acids **1**, by application of a new method that uses complexes of iodine monochloride and various primary amine ligands, such as (*R*)-1,2,3,4-tetrahydro-1-naphthylamine **2**. Selectivities of up to 50% *ee* were obtained in the iodolactones **3**.



A number of amines have been synthesised or acquired and tested as chiral ligands in this reaction. Although, in most cases, enantomeric excess has been observed in the product, none have performed better than the commercially available 1,2,3,4-tetrahydronaphthyl-1-amine.

Calculations were performed on complexes of (*R*)-1,2,3,4-tetrahydro-1-naphthylamine with XCl (X=I, H) to identify possible reactive species in these iodocyclizations. Various levels of theory were employed, including B3LYP/6-31+G (d,p) using a modified SDD basis set for iodine. Computational results suggest that, after initial complexation of the chiral amine with ICl, an exchange of iodine for a proton on the amine occurs. The HCl produced then forms a complex with a second amine molecule, which explains the need for two equivalents of amine in this reaction. Calculations also show that subsequent elimination of HI to form an imine is energetically favoured. This side reaction explains the presence of the corresponding ketone after work up and the decrease in enantioselectivity observed when the optimum complexation time of 30 min. before addition of the substrate is exceeded.

Abbreviations

a.u.	Atomic Units
Ac	Acetyl
AIBN	2,2'-azo-*bis*-isobutyronitrile
AM1	Austin Model 1
Ar	Aromatic
B3	Becke's 3 Parameter Functional
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
CCM	Continuous Chirality Measurement
CLEC	Cross-Linked Enzyme Crystals
DBU	1,8-diaza[5.4.0]bicycloundec-7-ene
DCC	Dicyclohexylcarbodiimide
DFT	Density Functional Theory
DIP-Cl	Diisopinocampheylchloroborane
DMAP	4-(Dimethyl)aminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
DPPA	Diphenylphosphoryl Azide
ECP	Effective Core Potentials
ee	Enantiomeric Excess
EI	Electron Ionisation
eq	Equivalent
Et	Ethyl

EWG	Electron-Withdrawing Group
GC	Gas Chromatography
h	Hours
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared
J	NMR Coupling Constant
KS	Kohn-Sham
LDA	Lithium Diisopropylamide
LYP	Lee, Yang, Parr Correlation Functional
Me	Methyl
mp	Melting Point
MP2	2nd Order Møller-Plesset Perturbation Theory
MS	Mass Spectrometry
Ms	Methanesulphonyl
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance (spectroscopy)
PCM	Polarisable Continuum Model
Ph	Phenyl
PM3	Parametric Method Number 3
PPA	Polyphosphoric Acid
SCRF	Self-Consistent Reaction Field
TBAB	Tetrabutylammonium Bromide
TEA	Triethylamine
THF	Tetrahydrofuran

TLC	Thin Layer Chromatography
TMS	Trimethylsilyl

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Chapter 1

Introduction

1.1 Lactones and Lactone Synthesis

Lactones are important substructures in many natural and pharmaceutical products. For example 3a,4,5,7a-tetrahydro-3,6-dimethyl-benzofuran-2(3*H*)-one is responsible for the sweet coconut smell in many white wines, hence its more common name, the wine lactone (fig. 1.1).[1]

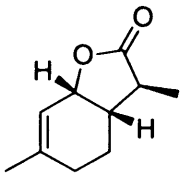


Fig 1.1 The wine lactone

This natural product, which can also be isolated from black pepper, is just one example of a whole range of naturally occurring lactones known to be important flavour and aroma constituents.

A whole family of antibiotics, the macrolide antibiotics, based on Erythromycin (fig. 1.2) first isolated from a soil fungus by in 1952, are all macrocyclic lactones.[2]

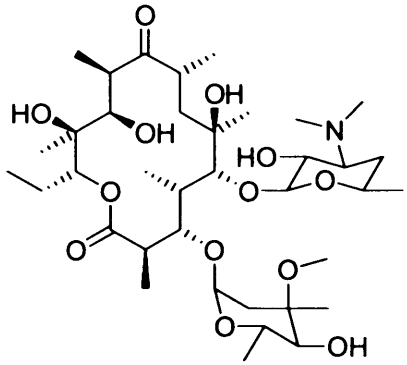


Fig. 1.2 Erythromycin

Vernolepin, a tumour-inhibitor isolated from Veronia Hymenolepis (fig. 1.3), is an example of a substance incorporating both a γ-lactone and a δ-lactone in a tricyclic sytem.[3]

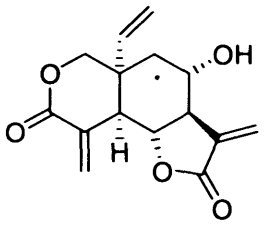


Fig. 1.3 Vernolepin

These are only a few examples, illustrating the variety, both in structure and applications, of naturally occurring lactones. The preparation of lactones can be performed in a number of ways. The simplest synthesis of lactones is achieved via the acid-catalysed condensation of hydroxycarboxylic acids (fig. 1.4).

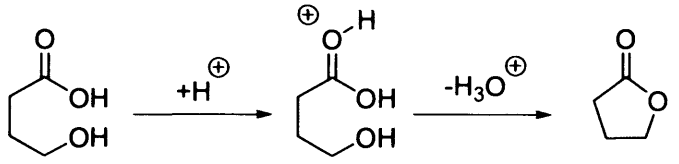


Fig. 1.4 Acid-Catalysed Condensation of Hydroxycarboxylic Acids

For five- and six-membered ring systems where there is little ring strain and few inter molecular interactions, such acid-catalysed processes are very efficient and yields lie between 90% and 95%. However, for larger molecules, yields drop dramatically as the reaction is reversible and is in competition with polymerisation. Although this is also the case for five- and six-membered rings, ring closure is far more energetically favourable in smaller systems. The intramolecular reaction may be promoted at low concentration but yields remain very poor. Yields can be improved by the use of intramolecular transesterification methods and the formation of mixed anhydrides. Such strategies are used in the Keck[4] and the Yamaguchi[5] macrolactonisation procedures. The Keck procedure uses dicyclohexylcarbodiimide (DCC), which reacts with the acid moiety of the uncyclised molecule to form an activated ester. Subsequent attack of the alcohol moiety leads to formation of the lactone and release of 1,3-dicyclohexylurea. The Yamaguchi macrolactonisation employs 2,4,6-trichlorobenzoyl chloride, which again reacts with the acid moiety to form a mixed

anhydride. Upon cyclisation via the alcohol, 2,4,6-trichlorobenzoic acid is released. The reagents and corresponding activated esters are shown in the figure 1.5.

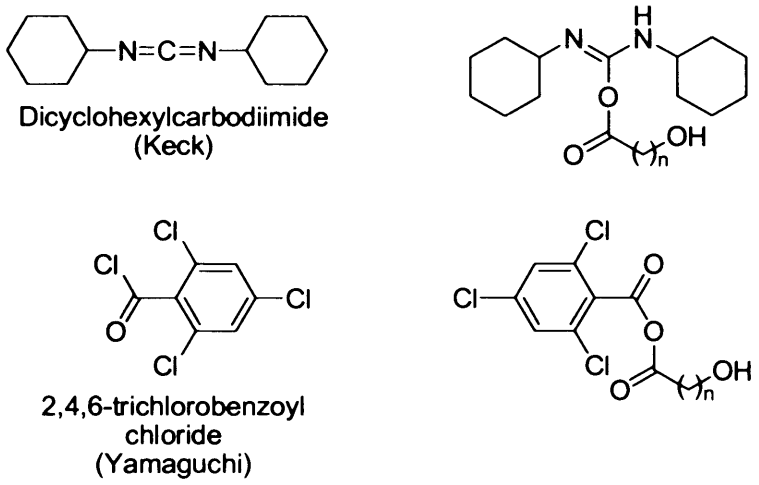


Fig 1.5 Keck and Yamaguchi Macrolactonisation Procedures

Like most natural products, naturally occurring lactones with chiral centres are generally only biologically active in one enantiomeric form, thus driving the need for methodology to carry out these lactonisations stereoselectively. A good example of a stereoselective synthesis of a lactone carried out using a naturally occurring catalyst is the reaction of meso-diols catalysed by an alcohol-dehydrogenase from horse liver shown in figure 1.6.[6]

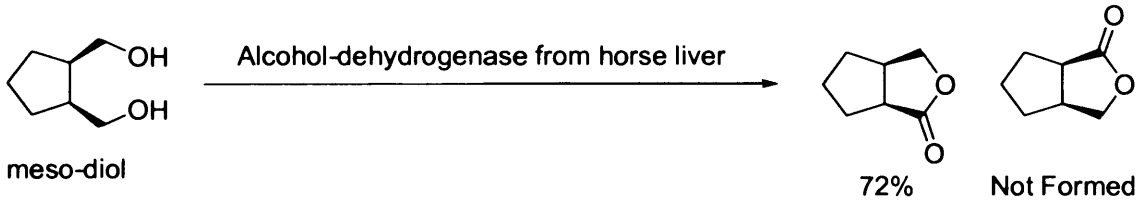
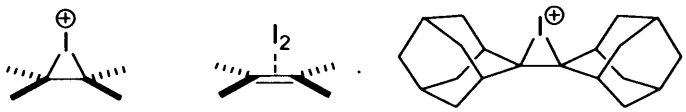


Fig 1.6 Example of a Stereoselective Reaction using a Natural Catalyst

1.2 Iodo-cyclisations

The addition of iodine electrophiles to alkenes, followed by either an intermolecular or intramolecular nucleophilic attack, is a strategy adopted in wide variety of syntheses. When an internal nucleophile is employed, a cyclised product is obtained.

Depending on ring size and stereochemistry either the *exo* or the *endo* product can be formed. The structure of the intermediate formed in the first step of the reaction, through the interaction of the iodine with the π-system of the alkene, is key to the stereochemistry observed in the product and has been the subject of many investigations. In 1937 Roberts and Kimball suggested a three-membered ring iodiranium type intermediate **1**, to account for the *trans*-stereochemistry observed in halogenations of double bonds.[7] Kinetic studies carried out on the iodocyclization of alkene thioethers seem to indicate an iodine–π complex **2** rather than a cyclic iodonium ion.[8] However, the isolation of stable iodonium ions such as **3** shows that both structures are possible and that the structure of the intermediate is dependent on both the alkene and the source of the iodine electrophile.[8] In both structures (fig. 1.7) the iodine atom effectively blocks one face of the double bond to nucleophilic attack, forcing a *trans* addition and making this type of reaction an ideal candidate for stereoselective syntheses.



1 **2** **3**

Fig 1.7 Proposed Structures of Iodonium Ions

Traditional reaction conditions, developed early in the last century, using a basic solution of elemental iodine **4**, potassium iodide and a base are often used today.[9] However, a wide range of different sources of I^+ are available to the organic chemist. For less reactive substrates, commercially available iodine monochloride **5** or monobromide **6**, with reactivities greater than two orders of magnitude higher than that of elemental iodine can be employed. Iodonium acetate **7**, *N*-iodosuccinimide **8**, or bispyridine iodonium tetrafluoroborate **9** and even stable iodonium ions, such as **3** have been investigated.[10]

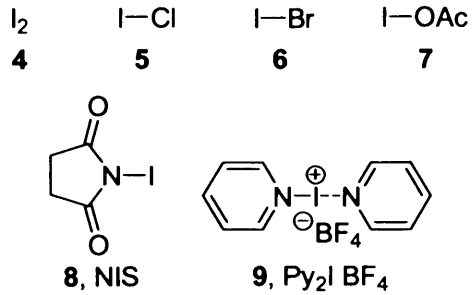


Fig 1.8 Sources of Electrophilic Iodine

The regiochemistry of simple electrophilic additions is controlled by electronic factors (Markovnikov's rule) and by steric factors. A general preference for *exo* cyclisations over *endo* cyclisations, in accordance with Baldwin's rules, can be observed. Several steps in the addition reactions may be reversible under the reaction conditions, so it is not always clear whether kinetic or thermodynamic control leads to the stereochemistry observed. Oxygen is probably the nucleophile used most frequently in such reactions, but nitrogen, sulphur and carbon nucleophiles can be used giving access to a range of differentially substituted compounds. Carboxylic acids and their derivatives (esters and amides) are the most commonly used as internal nucleophiles in such reactions. When a carboxylic acid is employed a lactone is formed.

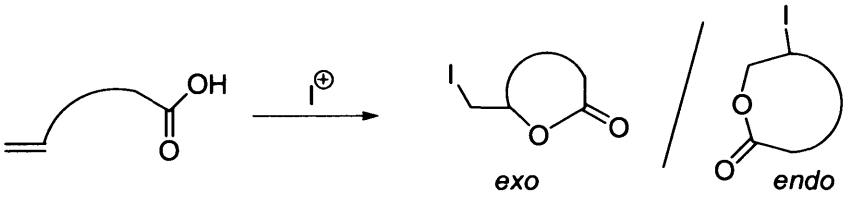


Fig 1.9 Iodocyclisations of Carboxylic Acids

Amides generally cyclise via the oxygen, which leads to lactones also being formed after hydrolysis of the imidate (both *exo* and *endo* products are formed but only the *exo* cyclisation is shown in figure 1.10).

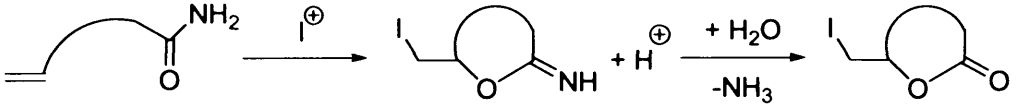


Fig 1.10 Formation of Lactones from Amides

It is, however, possible to form the lactams, the nitrogen containing analogues of lactones, by increasing the nucleophilicity of the nitrogen. This is usually achieved either by attaching an electron-withdrawing group (EWG) to the nitrogen, typically forming carbamates, *N*-acylamides and sulphamides,[11] or by forming stabilised imidates by treatment of amides with TMS chloride, usually *N,O*-bis(trimethylsilyl)imidates (figure 1.11).[12] Direct formations of lactams from amines, using metal salts such as mercury (II) chloride,[13] have also been reported.

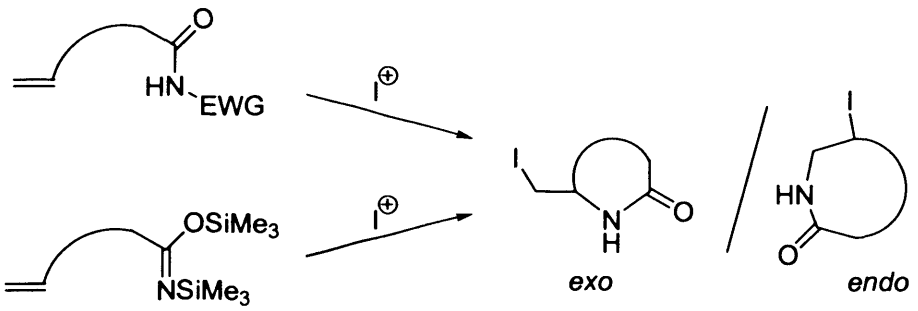


Fig 1.11 Lactam Synthesis

As well as producing products with relatively predictable stereo- and regioselectivity, the incorporation of the iodine into the molecule provides the possibility of further functionalisation via a wide range of different reactions. In addition to simple deiodination the iodine can be subjected to nucleophilic attack, employed in radical reactions, or eliminated to form double bonds, which can then be further functionalised and employed in coupling reactions. It is, therefore, no surprise to find such structures as intermediates in a wide range of natural product and other target syntheses.

1.2.1 Substrate-Controlled Reactions

In a substrate-controlled reaction a chiral centre present within the substrate dictates the chirality of a new centre formed during a reaction. This chiral centre can either be an integral part of the substrate or part of a chiral auxiliary. Many examples of the use of substrate-controlled, stereoselective iodocyclisations have been reported in literature. We have already published a review on the subject and some selected examples are described here.[14]

P. Metz and co-workers developed a method for the iodocyclisation of *N*-binaphthyl amides **10**. After addition of iodine, cyclisation occurs via the oxygen to form the cyclic imidate, which is hydrolysed in an aqueous workup. The binaphthyl group acts as a chiral auxiliary and is removed during the reaction. Selectivities of between 28% and 72% *ee* were obtained depending on the substrates (figure 1.12). It is not clear from the publication to what extent the two chiral centres already present in the

molecule play a role in the chirality of the subtrate. The disadvantage of this approach of using an auxiliary is the relatively large distance between the chiral centre and the reaction centre. In addition, the fact that the auxiliary must previously be attached to the substrate and in some cases removed after reaction, adds an extra step, which may have a detrimental effect on yield. [15]

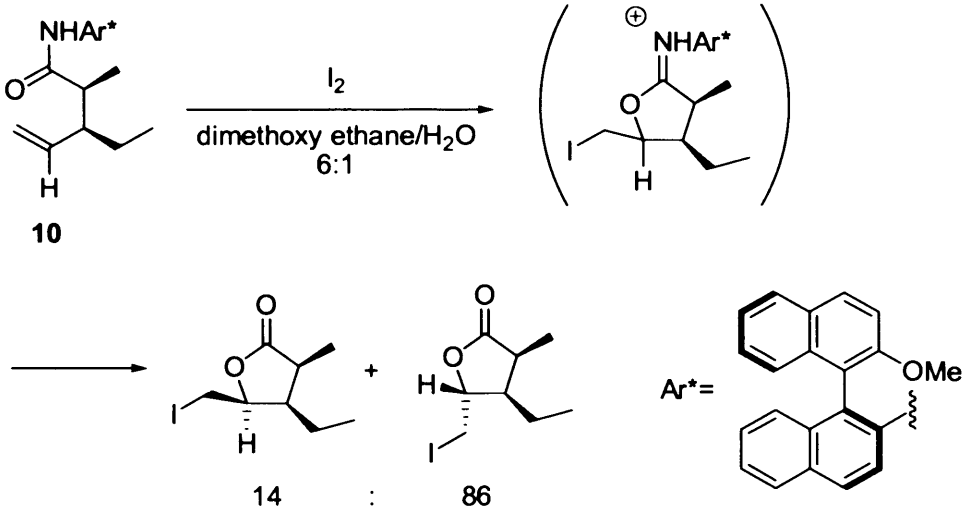


Fig 1.12 Metz's Iodolactonisation of *N*-Binaphthylamides

Danishefsky and Birman employed a substrate-controlled 5-*exo* iodolactonisation in the total synthesis of (±)-merrilactone A **11**, a pentacyclic dilactone sesquiterpene, and potent neurotropic factor (figure 1.13). The second lactone moiety was synthesised from an alkenyl acid precursor, **12**.[16] The resulting dilactone was obtained as roughly 2:1 ratio of stereoisomers, **13** and **14**. The iodide of **13** was subjected to radical allylation to give **15** which was converted to the to the natural product **11** in six subsequent steps.

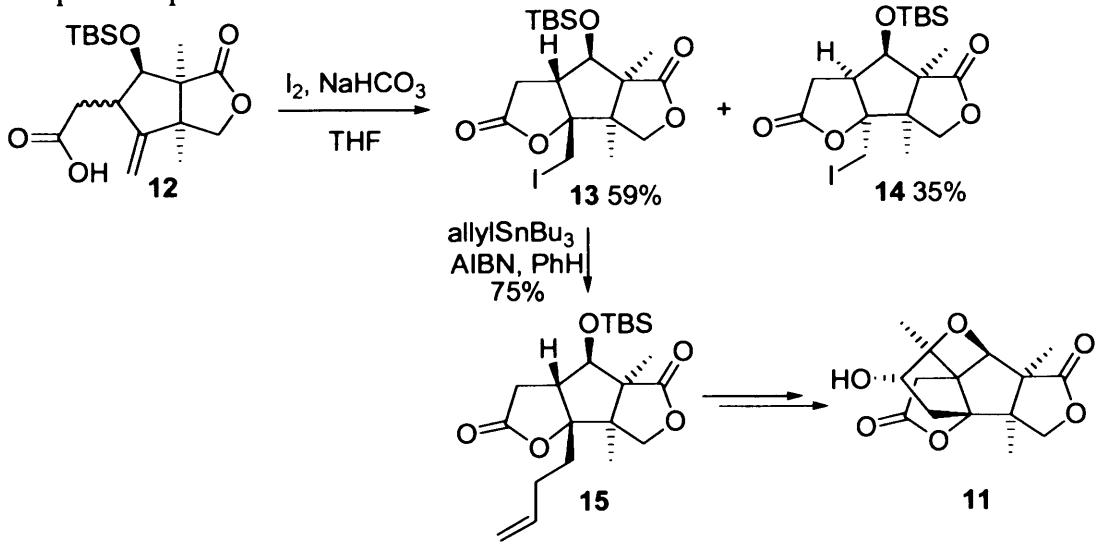


Fig 1.13 Danishefsky's Synthesis of Merrilactone A Intermediate **15**

In the total synthesis of (±)-Stenine **16**, a natural product isolated from the roots and rhizomes of stemonaceous plants, extracts of which have long been used in China and Japan as cough remedies, Ginn and Padwa carried out an iodo lactonisation on a γ,δ-unsaturated carboxylic acid (figure 1.14). Ester **17** was first cleaved with LiOH and the cyclisation was accomplished by treatment with iodine in acetonitrile. Subsequent radical allylation of iodide **18** lead to substitution of the iodine and to the formation of intermediate **19** with retention of stereochemistry due to steric hindrance.[17]

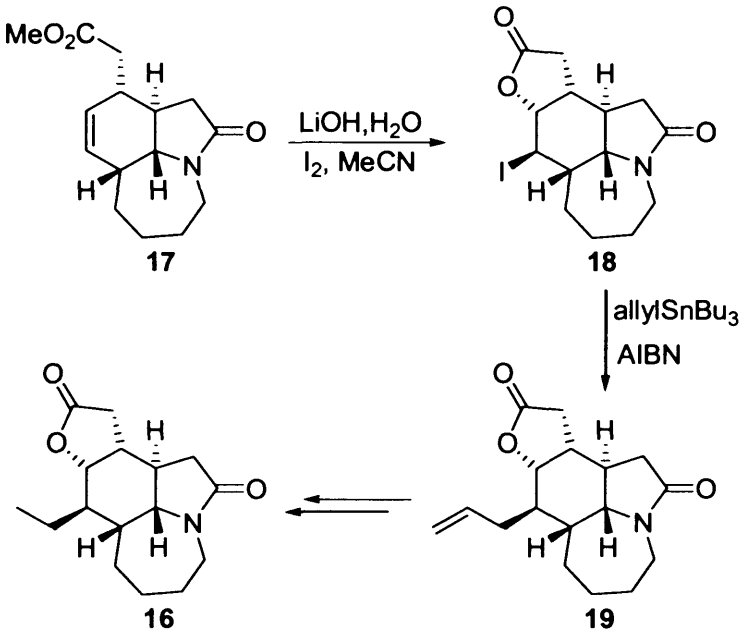


Fig 1.14 Ginn and Padwa's Total Synthesis of (±)-Stenine

Rozners and Liu performed an iodolactonisation of the unsaturated dimethylamide **20,** in their synthesis of an amide-linked RNA mimic (figure 1.15).[18] Sluggish reactions were observed when the corresponding esters were employed, however, good yields were obtained with the amide. The authors do not provide any explanation for this observation. A 4:1 mixture of *trans*:*cis* isomers of **21** was achieved, however, attempts to optimize this reaction with respect to this ratio failed, suggesting a thermodynamically controlled reaction. The resulting iodide was substituted with azide in good yield to give **22.**

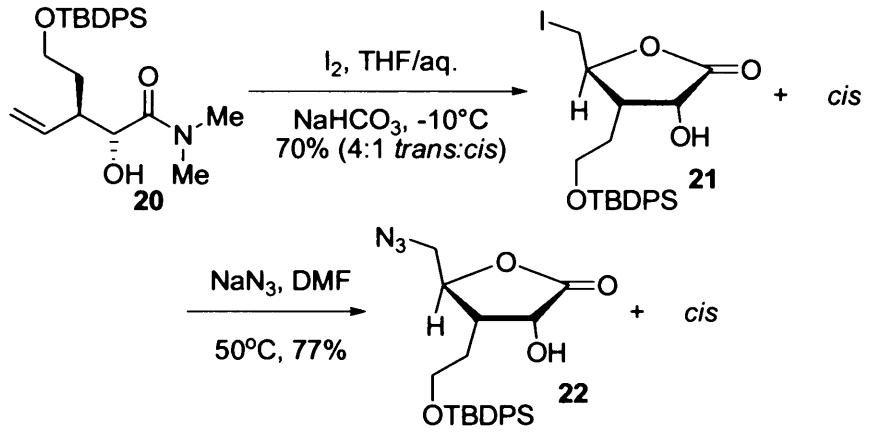


Fig 1.15 Rozners and Liu's Amide-Linked RNA Mimic

In the synthesis of mycotoxin FB_2 **23,** Kishi and coworkers used a 6-*exo* iodolactonisation of chiral unsaturated acid **24** to lactone **25** to set up two new stereogenic centres in a high diastereomeric ratio (>20:1), as the originaly planned Sharpless asymmetric dihydroxylation of the corresponding (*Z*)-alkene failed completely (1:1 dr) (figure 1.16). Therefore, in order to obtain the correct stereochemistry, it became necessary to replace the iodine by an oxygen atom with simultaneous inversion of both stereogenic centres. The lactone was opened with sodium benzylate, which underwent a subsequent epoxide formation by displacement of the iodide. The benzyl ester was then cleaved by hydrogenolysis, resulting again in lactone formation with epoxide opening, to generate the building block **26** used for the synthesis of mycotoxin FB_2, **23**.[19]

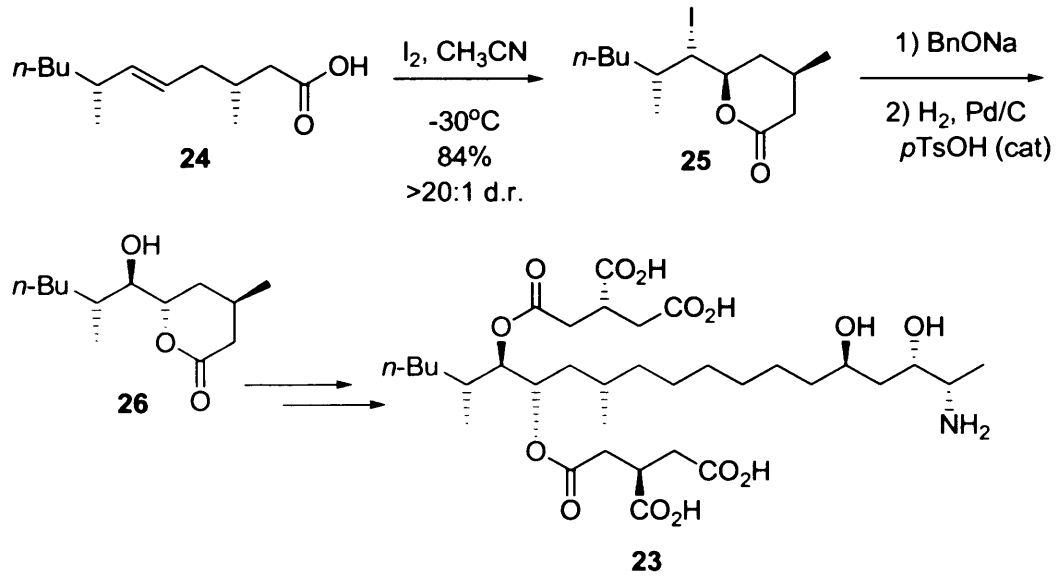


Fig 1.16 Kishi's Synthesis of Mycotoxin FB_2

Taguchi and co-workers demonstrated that excellent stereocontrol can be achieved in the iodocarbocyclisation of malonates[20] when titanium additives possessing chiral ligands are included in the reaction (figure 1.17). The practical utility of this methodolgy was proven by a number of syntheses, including the synthesis of (+)-boschnialactone **30** shown below. Treatment of malonate **27** with dimethoxypyridine (DMP), iodine and a chiral titanium ligand resulted in a 5-*exo* carbocyclisation to the *cis*-iodomethyl-cyclopentane **28** in 80% yield and 99% *ee*. Heating iodide **28** resulted in the cyclisation of the *cis* ester to give the lactone **29**, which was converted to the product in eight further steps. This reaction was found to be applicable only to substrates containing malonate functionality, as only malonates were found to coordinate efficiently to the $Ti(TADDOLate)_2$ complex, generating a chiral substrate-reagent complex which reacts with iodine in a stereoselective fashion.

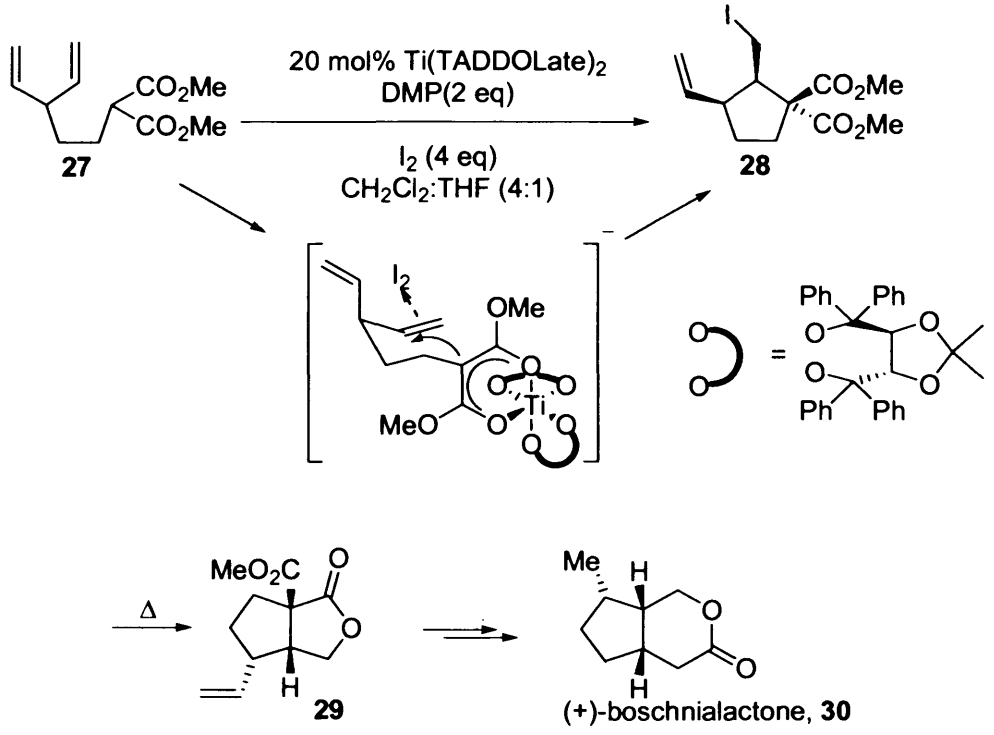


Fig 1.17 Taguchi's Synthesis of (+)-Boschnialactone

The strategy of coordinating chiral diols to titanium complexes has also been used in reagent-controlled reactions which are discussed below.

1.2.2 Reagent-Controlled Reactions

In reagent-controlled reactions, a chiral moiety in the reagent is responsible for the chirality observed in the product. Although they have valuable synthetic potential, there are only very few reports on chiral iodine electrophiles. Several chiral hypervalent iodine reagents are known, but chiral iodine(I) electrophiles have only recently appeared in literature. Chiral iodine(I) reagents can be formed by coordination of the iodonium ion to one or more chiral ligands. An early example of a reagent-controlled stereoselective iodocyclisation was published by Grossman and Trupp who prepared dihydroquinidine–iodine complex **31** as a source of a chiral iodonium ion (figure 1.18).[21] This reagent was employed in the cyclisation of a number of γ-δ-unsaturated carboxylic acids. Selectivities of up to 15% *ee* were achieved in the 5-*exo* iodolactonisation of (*Z*)-hept-4-enoic acid **32**. No selectivity was observed when the *E*-isomer was used as a substrate. Only negligible selectivities (7% *ee* and less) were observed for all other substrates tested in this reaction.

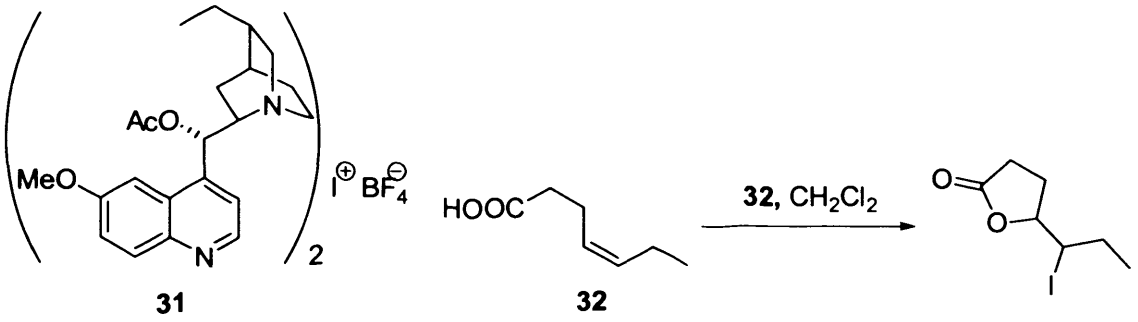
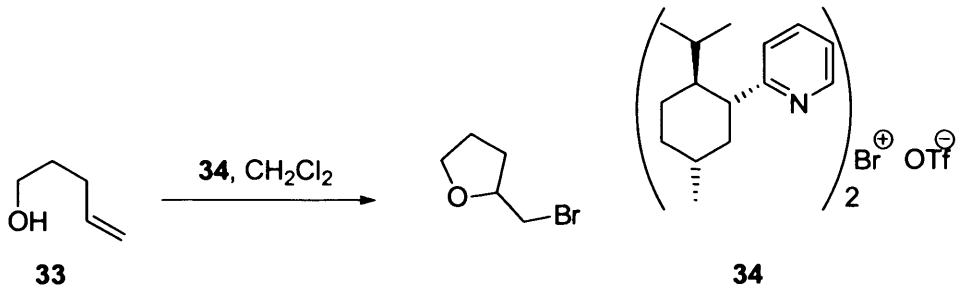


Fig 1.18 Grossmans Chiral Iodocyclisation Reagent

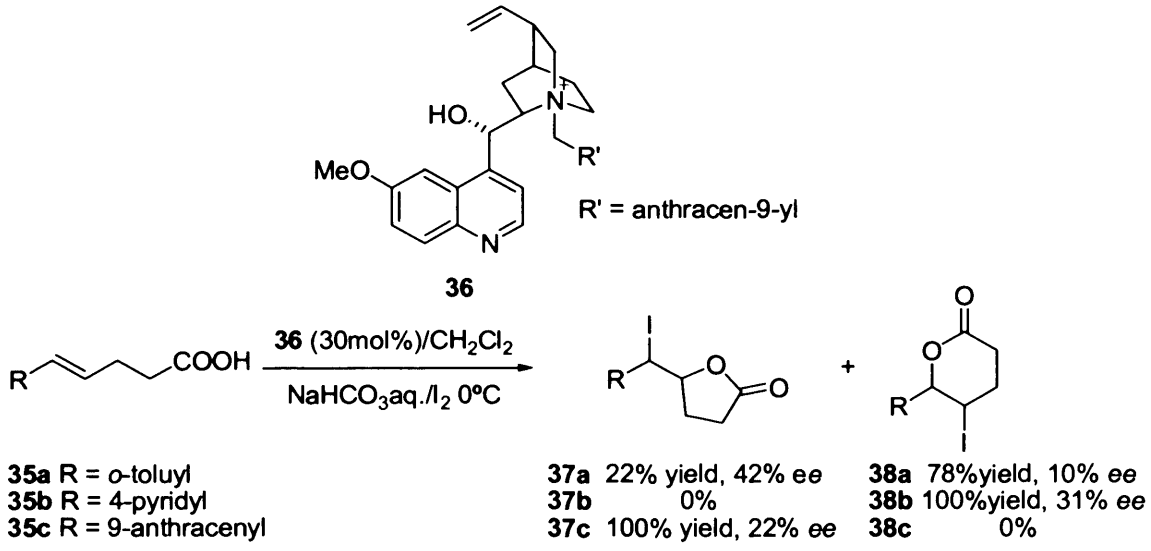
Brown and Cui investigated the bromocyclisation of 4-pentene-1-ol **33,** using modified pyridines as chiral ligands for Br^+.[22] Only minor selectivities (5% *ee*) were observed using the menthol derived pyridine complex **34** (figure 1.19). Kinetic studies suggest that, once the bromonium ion is formed, complexation of the chiral ligand to the alcohol moiety is responsible for the transfer of chirality. Further work on these types of systems has since been carried out by the Wirth group, which eventually led to the choice of chiral amine ligands in reagent controlled iodolactonisations, as described in the following chapter.[23]



33 34

Fig 1.19 Brown's Modified Pyridine Ligand

More recently Gao and co-workers have improved upon Grossman's original work using chiral, quarternary ammonium salts, derived from cinchonidine as phase transfer reagents in the iodolactonisation of *trans*-5-substituted-4-pentenoic acids **35a-c** (figure 1.20).[23] This is the first example of a catalytic reagent controlled iodolactonisation, as only 30 mol % of the chiral phase transfer reaction are required. The best selectivities observed were of 42% *ee* using ammonium salt **36** and *trans*-5-*o*-toluyl-4-pentenoic acid **35a**. The choice of catalyst not only had an effect on enantioselectivity but also on regioselectivity. A number of differently substituted acids were employed in reactions with **36**, but no apparent pattern was observed for the selectivity towards either 5-*exo* or 6-*endo* cyclisation. However, stereoselectivities generally appeared to be higher in the minor product. With *trans*-5-pyridine-4-yl-4-pentenoic acid **35b** exclusive formation of the 6-*endo* product **38b** was obtained and with trans-5-anthracen-9-yl-4-pentenoic acid **35c,** the 5-*exo* product **37c** was formed. In these two cases selectivities of 31 and 22 % *ee* were observed.



35a R = *o*-toluyl
35b R = 4-pyridyl
35c R = 9-anthracenyl

37a 22% yield, 42% ee
37b 0%
37c 100% yield, 22% *ee*

38a 78%yield, 10% *ee*
38b 100%yield, 31% *ee*
38c 0%

Fig 1.20 Wang's Chiral, Quarternary Ammonium Salt

Kang and coworkers have recently published another catalytic reagent controlled iodocyclisation (figure 1.21).[24] Preliminary results using chiral BINOL-Ti(IV) complexes in conjunction with NIS in the enantioselective intramolecular iodoetherification of γ-hydroxy-(*Z*)-alkenes **39** to yield 2-substituted tetrahydrofurans showed that a certain degree of selectivity could be obtained with up to 65% ee observed in the product.[25] Further experiments were carried out with chiral salen–cobalt complexes **40**. In addition, it was found that the addition of *N*-chlorosuccinimide further increased selectivities. Again, the choice of solvent seems to play a crucial role and reactions in toluene gave products **41** with up to 90% *ee*.

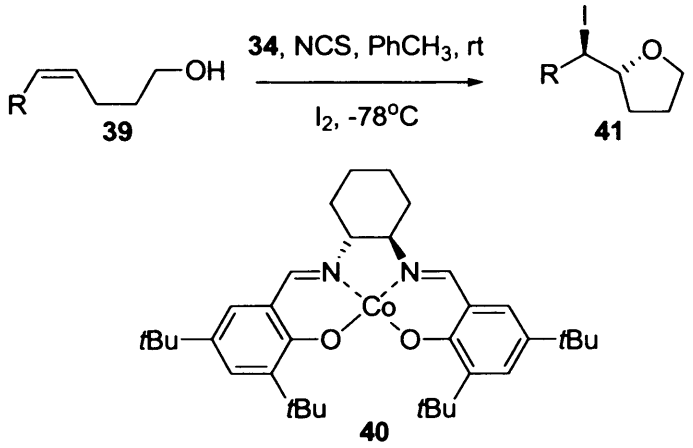


Fig 1.21 Kang's Catalytic Reagent Controlled Iodocyclisation with Chiral Salen–Cobalt Complexes

Although this method appears to be very efficient, it is extremely substrate specific, as the salen-cobalt complex is quite labile. This system is therefore not suitable for the lactonisation of carboxylic acids or molecules containing acid moieties.

Chapter 2

2. Project Aims

The work presented here focuses on a process developed by Wirth and co-workers, who studied the reagent-controlled iodolactonisation of 4-aryl-4-pentenoic acids **42**, using ICl and chiral primary amine ligands such as **43** (figure 2.1).[26] Electron deficient aryl groups gave improved selectivities suggesting a tighter association of the chiral amine–ICl complex to an electron deficient alkene. Up to 50% *ee* was obtained in the iodolactones **44**. A study on solvent effects was also carried out and methylenechloride was found to yield significantly higher selectivities than other solvents.

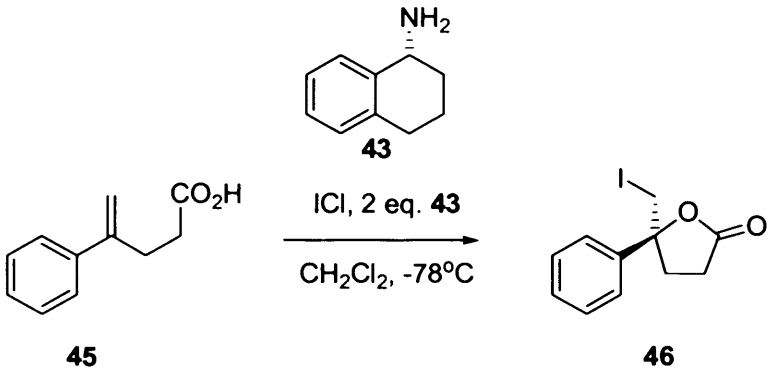


Fig 2.1 Wirth's Reagent-Controlled Iodolactonisation Employing a Chiral Amine Ligand

The aims of this project were to synthesise and evaluate new chiral amine ligands, investigate alternative ligands and electophiles and carry out cyclisation reactions with new substrates. In order to support and direct the experimental work, detailed computational analyses of the interactions between ICl and chiral amine ligands were also performed.

Chapter 3

3. Synthetic Results and Discussion

3.1. Chiral Amine Synthesis

The reaction conditions for the cyclisation reaction of 4-phenyl-pent-4-enoic acid **45** with ICl in the presence of 1,2,3,4-tetrahydronaphthyl-1-amine **43** have previously been optimised with respect to concentrations and the complexation time of ICl to the amine.[27]

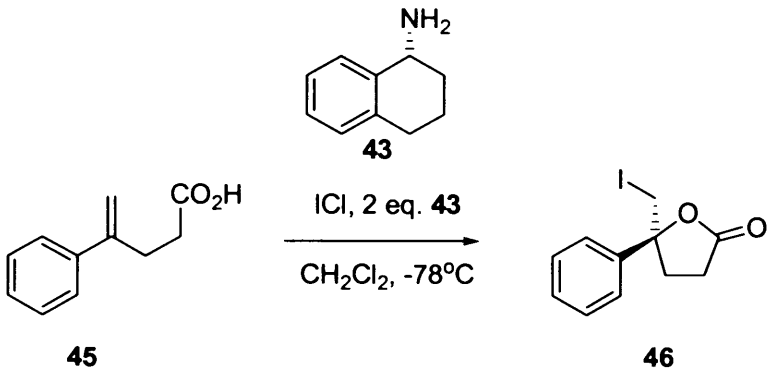
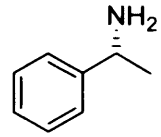
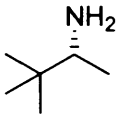
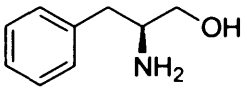
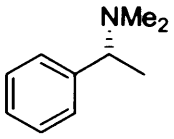
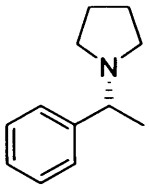
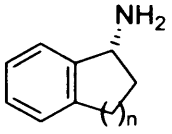
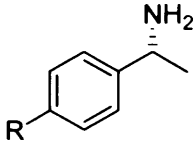


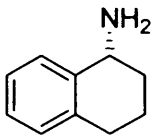
Fig 3.1 Cyclisation of 4-Phenyl-pent-4-enoic **45**

It was found that the amine and ICl must be allowed to stir for 30 min before cooling to -78°C and addition of the substrate in order to obtain optimal selectivity. Substrate **45** has been has been employed as a standard and a number of commercially available chiral amines have already been tested as ligands in this reaction and the results are shown in table 3.1. A number of trends can been observed.[27,28] Primary amine ligands led to higher selectivities than secondary amines, which, in turn, perform better than tertiary amines. The presence of an aromatic moiety in a 1,2 position relative to the amine functionality also seems to be an important for achieving high selectivities. A number of amino alcohols derived from naturally occurring amino acids have also been tested and no selectivity was observed. Protected amines also lead to little or no selectivity. These trends are illustrated by the examples included in the table below.

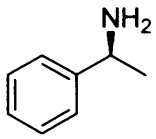
Table 3.1 Primary Amines used as Ligands in Stereoslective Iodolactonisations

Amine	*ee* (*R* or *S*)	Amine	*ee* (*R* or *S*)
	25% (*S*)		0%
	3% (*S*)		0%
	0%		13% (R)
	n = 1 18% (*R*) n = 2 45% (*R*) n = 3 10% (*R*)		R = Me 24% (*S*) R = NO_2 6% (*S*) R = OMe 10% (*S*)

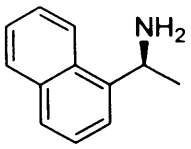
The best results to date were obtained using 1,2,3,4-tetrahydronaphthyl-1-amine **43** as a ligand, yielding an *ee* of 45% in iodolactone **46**. With 1-phenyl-ethylamine **47,** an *ee* of 26% is obtained and 1-naphthalenyl-1-ethylamine **48** leads to an *ee* of 29%. It was therefore assumed that, if the same improvement was observed with 1,2,3,4-tetrahydro-phenanthrenyl-4-amine **49**, high selectivity could be expected.[27]



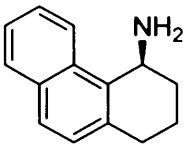
43



47



48



49

Fig 3.2 Chiral Amine Ligands

A number of derivatives of **43** were also chosen as targets in order to investigate the effects of different structural variations on stereoselectivity in iodolactonisations and are shown in figure 3.3. Amine **50** was chosen to investigate the effects of substituents on the aromatic system of the chiral amine ligand in the streoselective reaction. Amines **51** and **52** were chosen to ascertain whether or not increased steric hindrance, on the aromatic system in **51** and on the saturated system in **52**, would lead to an increase in stereoselectivity.

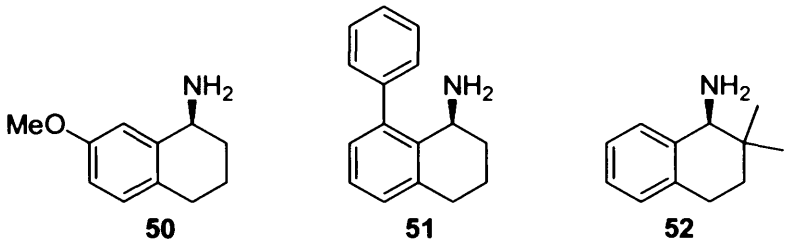


Fig 3.3 Other Proposed Targets Based on 1,2,3,4-Tetrahydronaphthyl-1-amine

When the standard cyclisation reaction with 1,2,3,4-tetrahydronaphthyl-1-amine **43** is carried out, the amine cannot be recovered after the work-up, with aqueous sodium thiosulphate. Instead only tetralone **53** is found. This suggests that the amine ICl complex **54** undergoes a series of reactions as shown in figure 3.4. The exchange of iodine for a proton on the amine followed by the elimination of HI, would lead to the formation of imine **55** (this subject is discussed in further detail in the computational section). Subsequently hydrolysis of **55** in the aqueous work-up would then lead to the formaton of ketone **53**.

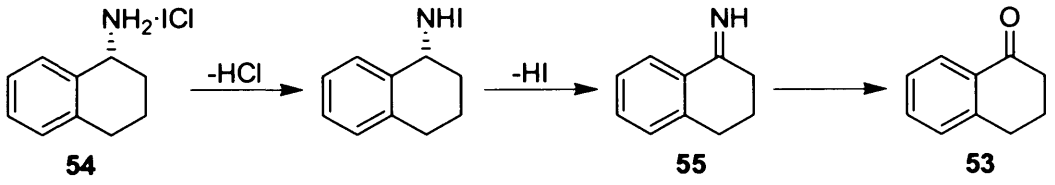
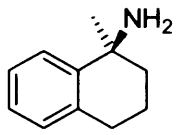


Fig 3.4 Proposed Route for the Decomposition of Amine-ICl Complexes

The decomposition of the amine ICl complex over time would also account for the observed decrease in enantioselectivity, when the optimal complexation time of ½ hour before addition of the substrate is exceeded and can be rationalised using the results of calculations.

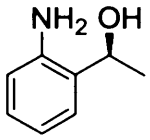
If an amine on a quaternary carbon centre could be synthesised, such an elimination would not be possible. Amine **56** was chosen as a suitable target because its structural similarity with 1,2,3,4-tetrahydronaphthyl-1-amine (figure 3.5).



56

Fig 3.5 1-Methyl-1,2,3,4-tetrahydronaphthyl-1-amine **56**

So far most ligands investigated have contained chiral centres directly next to the nitrogen.[27] In order to ascertain whether selectivity can be achieved using ligands with chiral centres in other parts of the molecule 1-(2-amino-phenyl)-ethanol **57** was also chosen as a target. This molecule was chosen because it contains a second heteroatom, which may chelate with the iodine bringing the chiral centre closer to the reaction center, thereby increasing the transfer of chirality.



57

Fig 3.6 1-(2-Amino-phenyl)-ethanol **57**

Ketones were chosen as starting materials in the synthesis of these molecules because they are easier to handle and are more stable than amines. The desired functionality was first introduced or obtained using a commercially available ketone. A number of methods were then attempted to introduce the amine functionality into the molecule.

3.1.1 Synthesis of 1,2,3,4-Tetrahydro-phenanthrenyl-4-amine

1,2,3,4-Tetrahydro-phenanthrenyl-4-amine **49** has already been synthesized as an intermediate by William H. Pirkle and coworkers, but as has not so far been isolated and fully characterised, being used in further reactions without purification.[29] It is in

fact a derivative of this compound, developed by the same research group, which is used in the synthesis of the stationary phase in the Whelk-O1 chiral HPLC column.[30]

The starting material for the synthesis of this amine, 4-oxo-1,2,3,4-tetrahydrophenanthrene **58c**, was prepared according to a modified literature procedure as shown in figure 3.7.[31] Naphthalene **59** was first treated with succinic anhydride **60** in a Friedel-Crafts acylation to give the two regioisomers of 4-naphthyl-4-oxobutanoic acid **61a/b**, in a ratio of 17:3 and 56% yield. The ketone functionality was then removed in a Wolff-Kishner reduction with hydrazine monohydrate in the presence of potassium hydroxide.[32] This procedure was chosen in preference to the Clemmensen reduction used in the original literature as it avoids the use of mercury and was found to be higher yielding. The resulting 4-naphtylbutanoic acids **62a/b** (obtained in 78% yield as opposed to 69%) were cyclised with polyphosphoric acid to yield two regio-isomers of **58**, which can easily be separated by column chromatography.[31] Two products, **58a** and **58b**, could be separated and were obtained in 76% and 13% isolated yield respectively; not surprisingly the same ratio was observed as that for **61a** and **61b**. Interestingly no trace of **58c**, which might be expected as a by-product from the cyclisation of **62a** was observed.

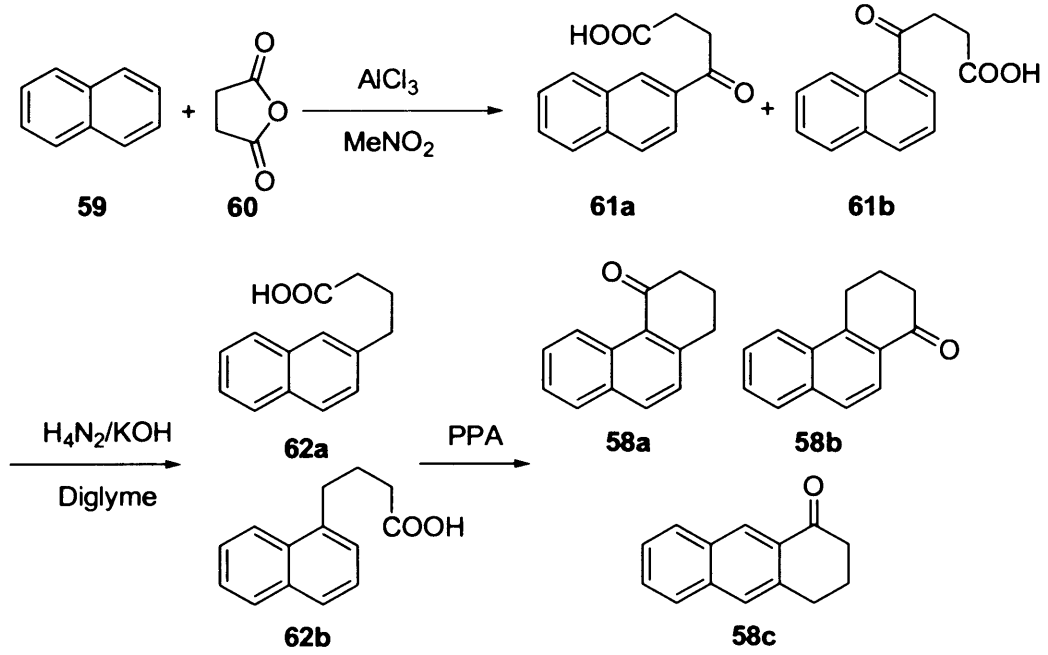


Fig 3.7 Synthesis of Ketone **58a**

The racemic amine **63** was then produced by reductive amination of the ketone **58a** with sodium cyanoborohydride and ammonium acetate in *iso*-propanol.[29] The reaction was found to be very sensitive to the presence of water, leading to the formation of

acetate **64** as a major by product (see figure 3.8). Even under optimised conditions, using dry *iso*-propanol and ammonium acetate dried at 95°C under vacuum for several hours, a significant quantity of acetate **64** was formed (the ratio of amine **63** to acetate **64** ranged from 7:3 to 2:3).

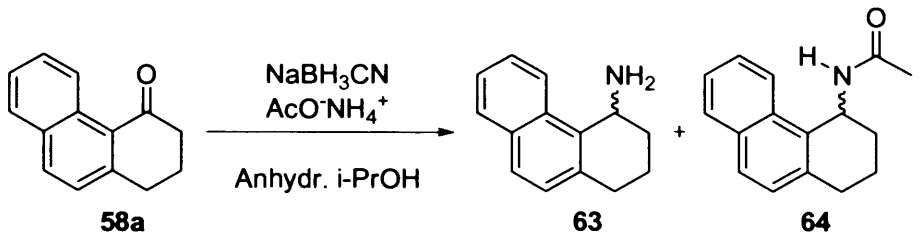


Fig 3.8 Reductive Amination of Ketone **58a**

In order to separate the enantiomers, the crude amine was further reacted with (1*R*, 2*S*, 5*R*)-(–)-menthyl chloroformate, to yield the diastereomeric carbamate **65**.[33]

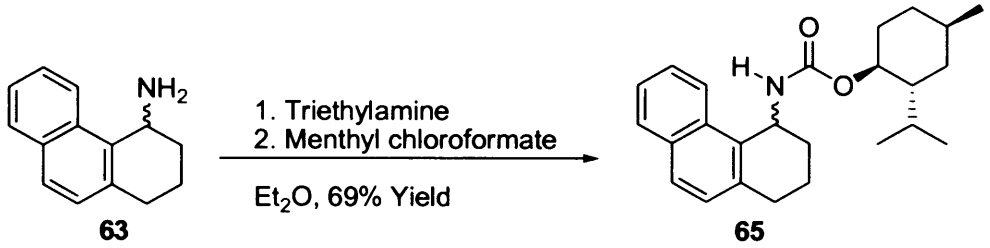


Fig 3.9 Synthesis of diastereomeric carbamate

As this product is a mixture of diasteriomers it should be possible to separate the two by column chromatography. Separation using the solvent mixture mentioned in literature[33] (6:1 Hexane:CH_2Cl_2) proved to be poor, so the enantiomerically pure material was obtained by separation on preparative HPLC on the Chiralcel OD column (95:5 Hexane:*Iso*-propanol). Attempts to cleave the carbamate under acidic and basic conditions using literature procedures proved unsuccessful, leading to loss of the product in the aqueous phase and subsequent decomposition. Cleavage with TMS iodide produced *in situ* led to the same result and reduction with lithium aluminium hydride only led to formation of the methylated secondary amine.

The crude amine was also allowed to react directly with 3,5-dinitrobenzoylchloride **66** to give the amide **67** in almost quantitative yield (figure 3.10).[29] This can again be separated by HPLC, using the same conditions as above, but the cleavage of this product also proved problematic. Again a number of acidic and basic conditions were employed with results similar to those observed with carbamate **64**. In order to follow

the reaction by NMR a basic hydrolysis with potassium deuteroxide, produced by addition of potassium superoxide to deuterated water was attempted. The reaction was carried out in a biphasic system with the amide dissolved in deuterated chloroform in a dry flask under argon. This allowed for direct analysis by NMR of both phases without further workup. Even after 24h, no trace of the amine was observed in either phase. Little or no organic material was present in the aqueous phase and starting material with traces impurities were observed in the organic phase.

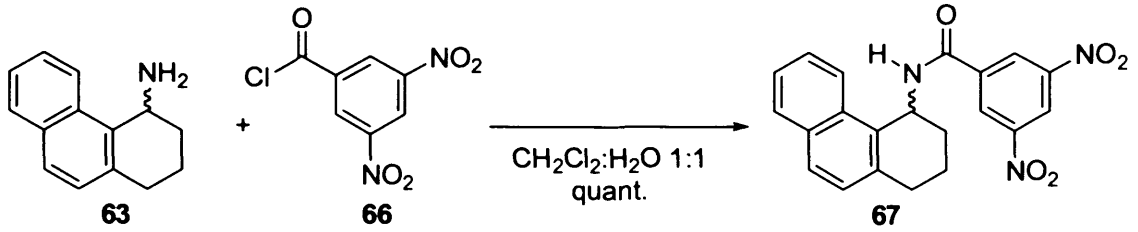


Fig 3.10 Synthesis of amide **67**

The same problems were encountered when trying to convert the Whelk-O1 olefin **68**, obtained from the Regis company, into the free amine (see figure 3.11). This compound was obtained in its enantiomerically pure form from Regis Technilogies but had first to be reduced to remove the double bond, which is usually used to link it to a solid support and would be susceptible to electrophilic attack in the presence of ICl. This was achieved by hydrogenation with Wilkinson's catalyst to yield amide **69**.[34]

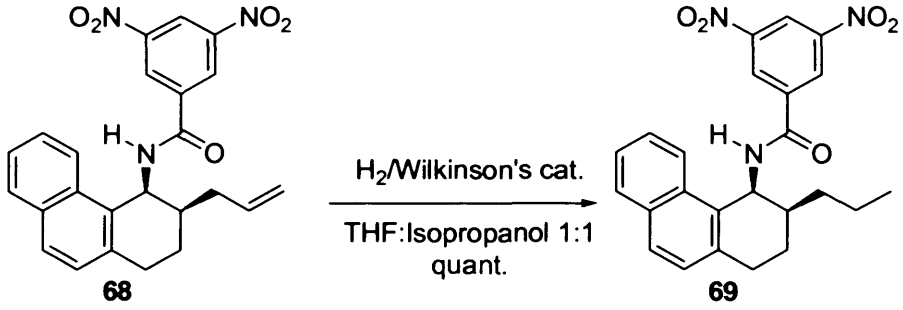
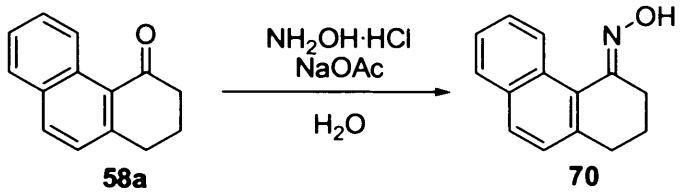


Fig 3.11 Reduction of the Whelk-O1 Olefin **68**

As the cleavage of these amine derivatives proved problematic, a different approach was adopted. The asymmetric reduction of oxime ethers with reagents prepared from borane and chiral amino alcohols is well documented in literature.[35] Oxime **70** was therefore synthesised from the reaction of ketone **58a** with hydroxylamine hydrochloride in the presence of a 1:1 mixture of sodium and potassium carbonate in

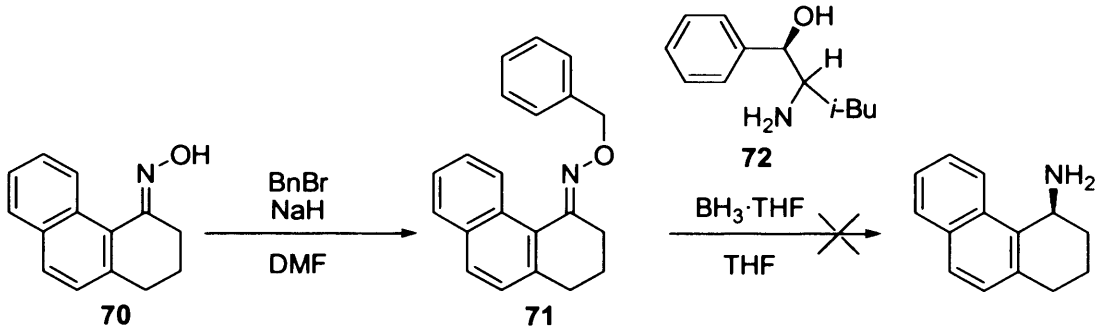
dioxane (figure 3.1).[36] Unfortunately, the yields from this procedure were poor so a more classic procedure using aqueous hydroxylamine hydrochloride solution was employed and the product was isolated in 85% yield.[37]



58a 70

Fig 3.12 Synthesis of Oxime **70**

The oxime was converted to the benzyloxime ether **71**, synthesised by treatment with sodium hydride and benzylbromide in DMF.[38] Unfortunately, attempts to reduce **71** asymmetrically with a complex of borane with chiral amino alcohol **72** failed.[38] A complex mixture of products and starting material was recovered, but the desired product was not observed by GC-MS.



70 71 72

Fig 3.13 Synthesis and Reduction Benzyloxime Ether **71**

If it was possible to carry out a stereoselective reduction on ketone **58a**, substitution of the resulting alcohol to the azide should yield the corresponding chiral amine after reduction. Diisopinocampheylchloroborane (DIP-Cl), a reagent developed by H. C. Brown,[39] was chosen for this reaction, as it has previously been employed for the asymmetric reduction of similar molecules. In his original work, Brown carried out a series of reductions on a number of α-phenyl ketones. More significantly, it was also shown that DIP-Cl can be employed to reduce cyclic ketones, such as 1-indanone and α-tetralone as well as for the reduction of α-naphthyl substituted ketones, in reasonable yields and with high selectivities. Some or the results of this work are shown in table 3.2.

Table 3.2 Results of Original Investigation into the Asymmetric Reduction of Ketones with (-)-Diisopinocampheylchloroborane

Ketone	Yield of Alcohol (%)	*ee* (%)
Acetophenone	72	98 (*S*)
1-Indanone	62	97 (*S*)
α-Tetralone	70	85.6 (*S*)
1-Acetonaphthone	90	98.1 (*S*)

Brown concluded that the reaction proceeds via a six-membered cyclic transition state, where the steric hindrance of the methyl group adjacent to the boron atom forces the larger substituent on the ketone away, thus favouring the attack on one face of the ketone over the other. This transition state is shown in the figure bellow.

Fig 3.14 Transition State in the Asymmetric Reduction of Ketones with DIP-Cl

These results suggest that DIP-Cl should be an ideal reagent for the asymmetric reduction of ketone **58a**. The first attempt to carry out the reduction was performed under standard reaction conditions at –25°C in THF[38] and failed. It has also been demonstrated that in the case of more sterically demanding ketones, it is sometimes necessary to carry out reactions in neat DIP-Cl at room temperature,[38] but even under these reaction conditions no reaction was observed.

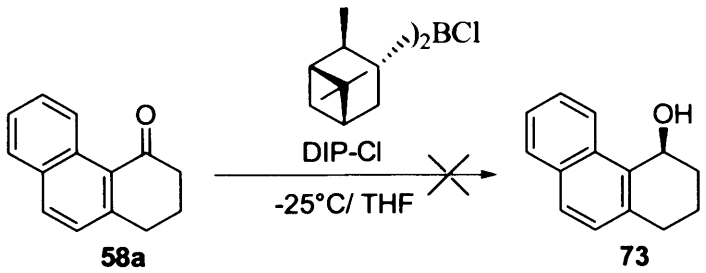


Fig 3.15 Asymmetric Reduction of Ketone **58a**

CLECs are cross-linked enzyme crystals.[40a&b] A natural enzyme (generally a lipase or esterase) is isolated and cross-linked. This is achieved by allowing pure enzymes to react with glutaraldehyde in water. The dialdehyde forms both intra- and inter molecular imine bonds with the free amine groups of lysine residues in the backbone of the enzyme as shown in the figure below. The degree of cross-linking is somewhat unpredictable as gluteraldehyde undergoes oligomerisation in aqueous media. However, it is possible to obtain reproducible results under carefully controlled conditions.

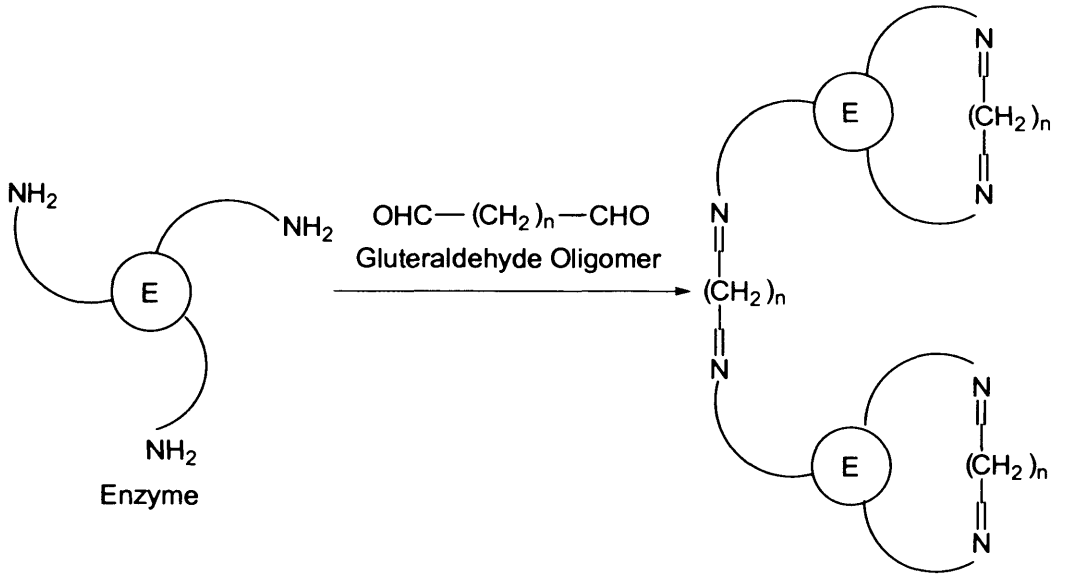


Fig 3.16 Schematic Representation of the Cross-Linking of Enzymes with Glutaraldehyde

The mechanism of cross-linking is not fully understood and is irreversible. The cross-linking locks the enzyme in its active conformation and renders it insoluble in both organic solvents and water. The enzyme crystals, which are normally very fragile become sturdy and robust. They can be used in organic solvents in a one-phase reaction and do not require precise pH control. Although very expensive, these catalysts can easily be recovered by filtration, washed and reused, loosing only very little of their activity.[40b] These catalysts can be used in the formation and cleavage of esters. They can be used for the kinetic resolution of racemic alcohols as they greatly enhance the rate of reaction of one enantiomer when compared to the other. In the best-case scenario the difference in the rate of reaction is so great that it is possible to

obtain a mixture of virtually enantiomerically pure alcohol and ester, which can be separated by chromatography.[40a]

The use of lipase from *Pseudomonas cepacia* for the kinetic resolution of secondary alcohols is well documented in literature. It has been used for the resolution of a number of 1-phenyl- and 1-naphthyl-ethanol derivatives.[40c] Cross-linked lipase from *Pseudomonas cepacia* was therefore chosen as the catalyst for the kinetic resolution of alcohol **73**.

To attempt such an enzymatic resolution, the ketone was first reduced to alcohol **73** with sodium borohydride.

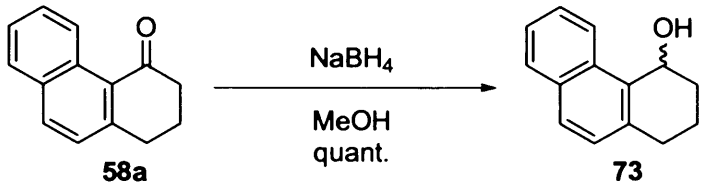


Fig 3.17 Sodium Borohydride Reduction of Ketone **58a**

In order to determine HPLC conditions for analysis of the enzymatic resolution it was first necessary to synthesise the racemate of acetate **74**. The acetate was formed in good yield (73%) from the reaction of the alcohol with acetyl chloride and a catalytic amount of DMAP.[41]

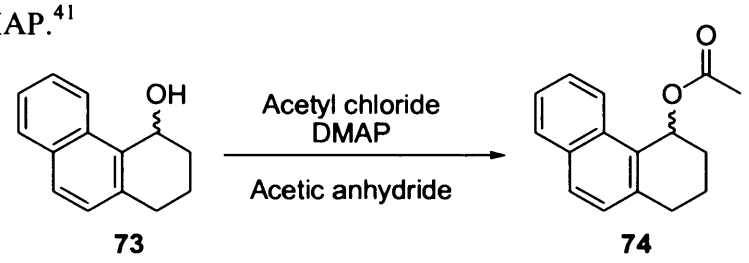


Fig 3.18 Acetylation of the Racemic Alcohol **63**

The alcohol was then allowed to react with vinyl acetate in the presence of Altus CLEC-PC® (lipase from *Pseudomonas cepacia*) in toluene as a solvent.[40a]

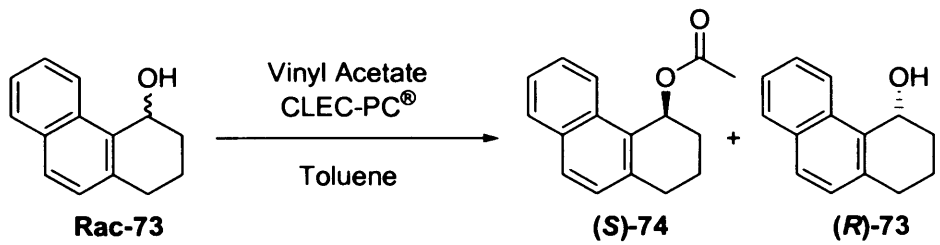
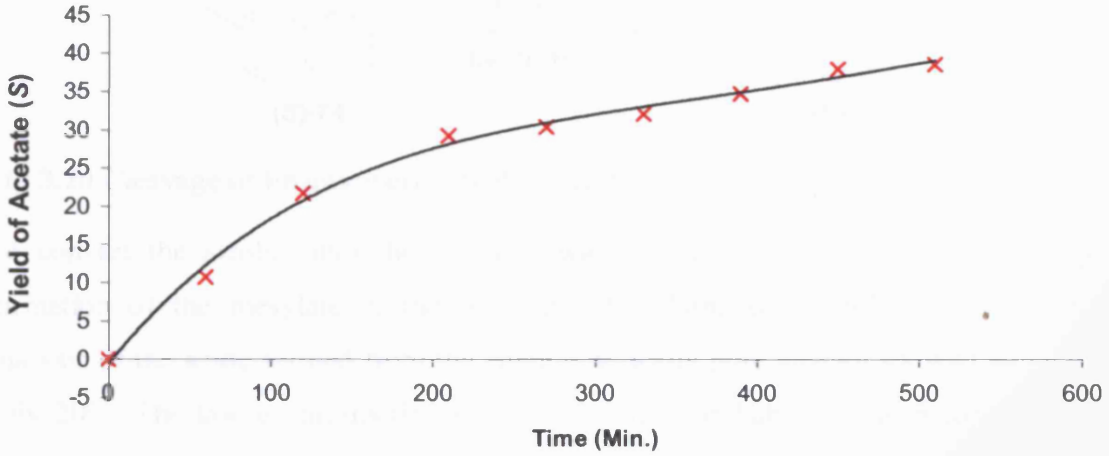
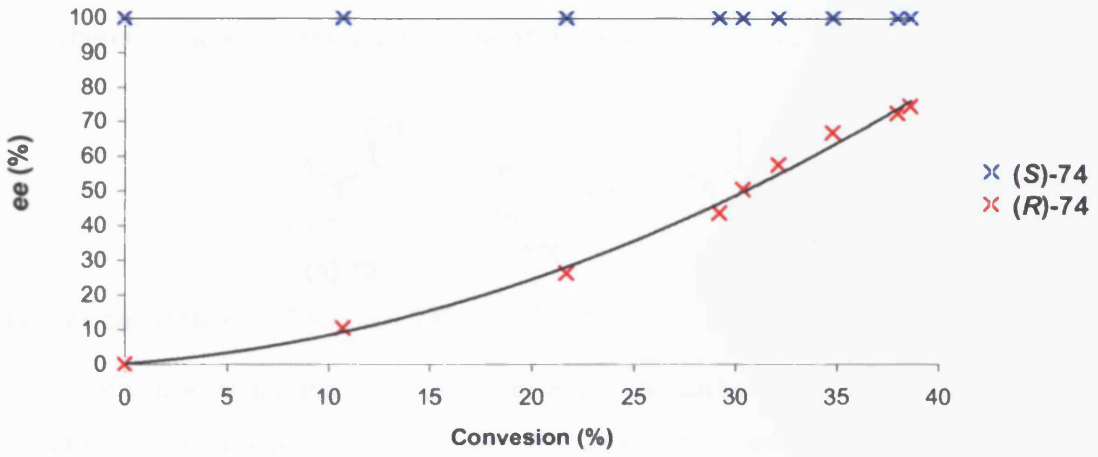


Fig 3.19 Enzymatic Resolution of Racemic Alcohol **73**

The reaction was first carried out on a small scale and monitored by HPLC, with the Chiralcel OD-H column (90:10 hexane/isopropanol) and the results are shown in the two graphs below.



Graph 3.1 Yield in Acetate (*S*)-74 over Time



Graph 3.2 Plot of Enantiomeric Excess against the Conversion of Alcohol to Acetate

Graph 3.2 shows that only one enantiomer of the alcohol takes part in the reaction, while the other does not react at all. Analysis of the acetate formed in the enzyme-catalysed reaction proved that it was indeed enantiomerically pure as determined by HPLC. The reaction was then repeated on a larger scale and the enzymes were removed before the second enantiomer started to react, in order to ensure that the acetate was enantiomerically pure. It was then necessary to cleave the acetate. This

was achieved, in quantitative yield, by reaction with potassium carbonate in aqueous methanol.[42]

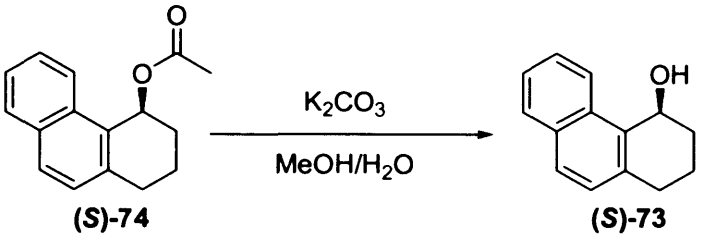


Fig 3.20 Cleavage of Enantiomerically Pure Acetate

To convert the alcohol into the amine it was first transformed into the azide by formation of the mesylate in the presence of sodium azide **75**.[43] Unfortunately, analysis of the azide formed from the enantiomerically pure alcohol showed an *ee* of only 20%. The low enantiomeric excess observed is probably due to a competition between S_N1 and S_N2 mechanisms, as the carbocation in the benzylic position is stabilised by delocalisation in the aromatic system. The use of diphenylphosphorylazide (DPPA) in the presence of DBU, chemistry similar to that of the Mitsunobu reaction, proceeded via an S_N2 mechanism with complete inversion of steriochemistry leading to the formation of the azide in 98% *ee*.[44]

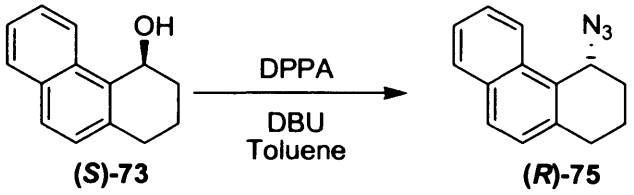


Fig 3.21 Substitution of Alcohol **73b** with DPPA

The azide is also much more soluble than either the carbamate or the dinitrobenzoyl derivative of the amine. It is, therefore, also possible to resolve the enantiomers by preparative, chiral HPLC. Yields in the reduction of the azide to the amine with hydrogen and palladium on charcoal appear to be dependent on the solvent used. Reactions in ethanol lead to decomposition of the product and no reaction is observed in THF alcohol mixtures. Reduction with diborane THF complex also leads to decomposition. The best results were obtained using hydrogen and palladium on charcoal in anhydrous methanol and the enantiomerically pure amine **76** was isolated in quantitative yield.[45]

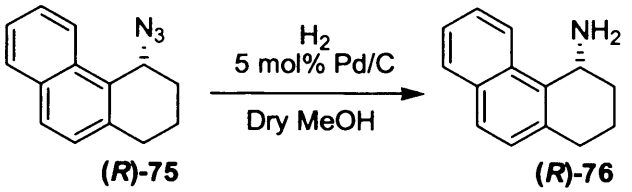


Fig 3.22 Reduction of Azide **75**

3.1.2 Synthesis of 7-methoxy-1,2,3,4-tetrahydronaphthyl-1-amine

As the enzymatic resolution method was so successful, the same strategy was employed for the synthesis of 7-methoxy-1,2,3,4-tetrahydronaphthyl-1-amine **50**. Alcohol **77** was prepared, in 98% yield, by reduction of commercially available 7-methoxy-1-tetralone **78** with sodium borohydride.

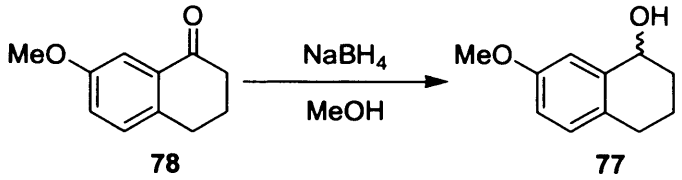


Fig 3.23 Reduction of 7-Methoxy-1-Tetralone **78**

The enantiomers were then separated by enzymatic resolution as described previously.[46] The configurations shown have been determined in previous work by the Wirth group.[46]

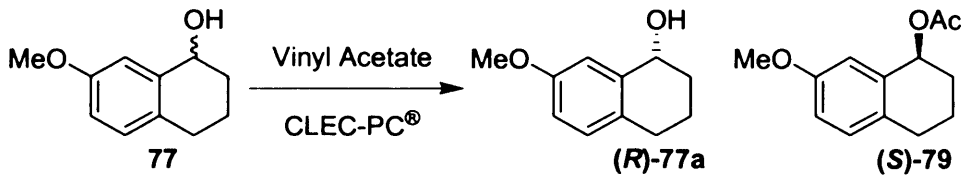


Fig 3.24 Resolution of 7-Methoxy-1,2,3,4-tetrahydronaphth-1-ol **77**

The reaction was monitored by HPLC and allowed to proceed until the alcohol was enantiomerically pure, as the acetate could not be analysed on a reasonable time scale, due to its short retention time (HPLC runs lasted only 15 min with a 90:10 hexane:isopropanol mixture, but at this polarity there was no baseline separation on

the acetate peak). The resulting enantiomerically enriched acetate can be purified by recrystallisation from diethyl ether. Reaction of the enantiomerically pure alcohol with diphenylphosphorylazide (DPPA) in the presence of DBU lead to the formation of the azide **80** in 68% yield.

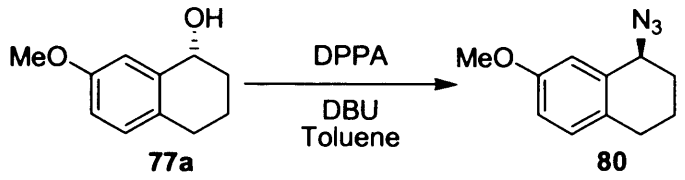


Fig 3.25 Synthesis of Azide **80**

Analysis of the product by HPLC showed that no racemisation had occurred during the course of this reaction. The azide was then reduced with palladium on charcoal and amine **50** was obtained in 38% yield. The low yield in this reaction is due to loss of product during purification, as it was difficult remove the amine from the silica.

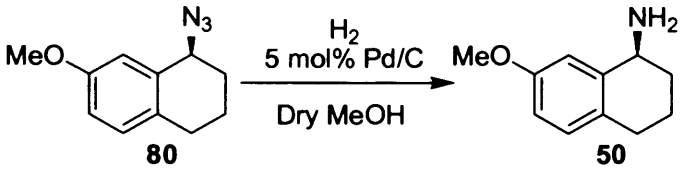


Fig 3.26 Reduction of Azide **80** to give the desired Amine

3.1.3 Attempted Synthesis of amines 51 and 52

In order to synthesise amine **51**, the ketone precursor, 8-phenyl-3,4-dihydro-2*H*-naphthalen-1-one **81,** had first to be prepared. A literature procedure was found for attaching phenyl rings in the *ortho*-position of aromatic carbonyl compounds, making **81** easily accessible from tetralone.[47] This involved a ruthenium catalysed coupling reaction with a boronic acid derivative. Phenyl boronate **82** was therefore synthesised via the condensation of phenyl boronic acid **83** with neopentyl glycol **84**. The product was obtained in quantitative yield by refluxing the reactants dissolved in toluene in a Dean-Stark trap. The product was then allowed to react with tetralone **53** in the presence of a ruthenium catalyst to form ketone **81**. Pinacol is used as an additive in

this reaction, as it prevents the reduction of one equivalent of the ketone. This not only increases the yield with regards to tetralone but also speeds up the reaction and prevents the formation of tetralol, which is difficult to separate from the product.[48]

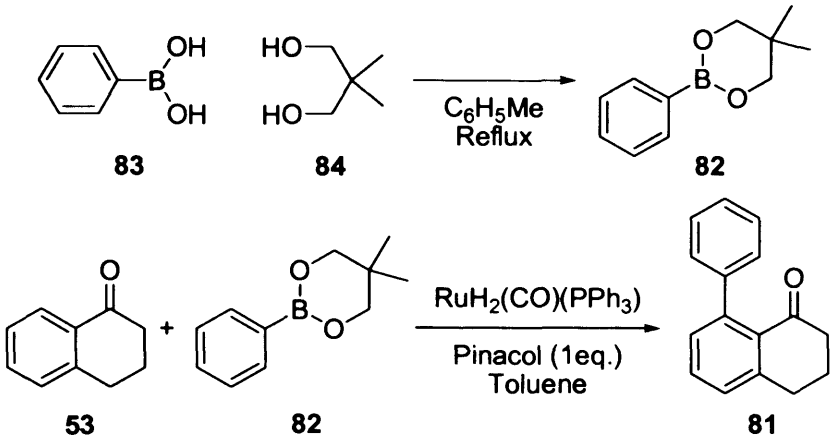


Fig 3.27 Coupling of Tetralone with Phenyl Boronate **82**

Unfortunately all attempts to incorporate nitrogen into **81** failed. Reductive amination using the same conditions as those used in the synthesis of **49** was unsuccessful and even after refluxing for several days only starting material was recovered. Condensation reactions with hydrazine and benzoylhydrazine under various conditions also lead to the recovery of starting material.

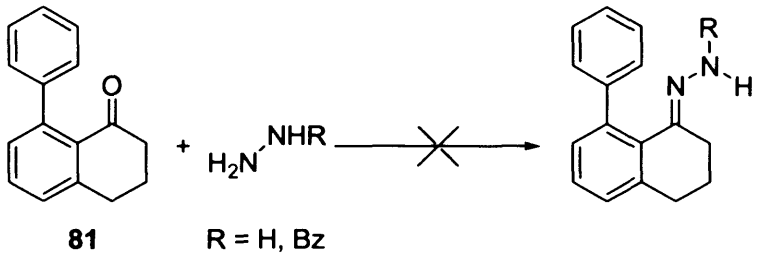


Fig 3.28 Attempted Synthesis of Hydrazone Derivatives

It was therefore decided to reduce the ketone to the alcohol, and attempt to follow the same synthetic route used for the synthesis of both **76** and **50**. Again, as DIP-Cl failed to reduce the ketone, racemic alcohol **85** was obtained in quantitative yield from the reduction of **81** with sodium borohydride.

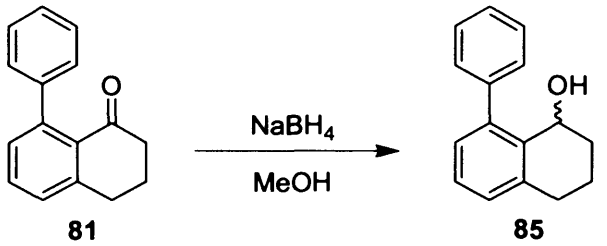


Fig 3.29 Reduction of ketone **85**

Alcohol **85** did not, however, react with vinyl-acetate in the presence of CLEC-PC enzymes and could therefore not be resolved via this method. Furthermore, formation of azide **86** through substitution of the alcohol proved problematic. Both the aforementioned methods of azide synthesis (mesylation in the presence of sodium azide and reaction with DPPA) failed to produce more than trace amounts of product and more than 95% of the starting material could be recovered from both reactions.

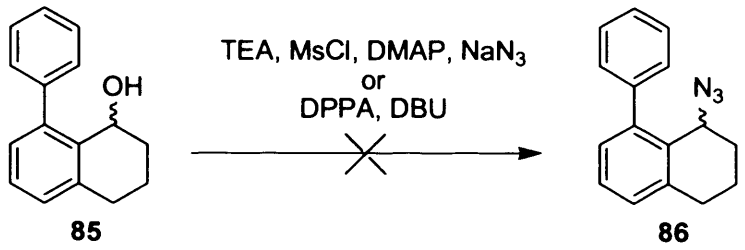


Fig 3.30 Attempted Synthesis of Azide **86**

These results are probably due to the fact that the carbonyl group of this molecule is extremely sterically hindered. The phenyl substituent in the *ortho*-position is in a plane orthogonal to that of the second aromatic ring, shielding the carbonyl group from nucleophilic attack. Furthermore, the unsaturated cyclic system effectively shields the other half of the molecule. In the case of the ketone, electronic effects, due to the conjugation of electrons with the aromatic system may also play a role in low reactivity.

Similar problems were encountered with 2,2-dimethyltetralone **87**, synthesised from tetralone by treatment with NaH and methyl iodide in 76% yield.[49]

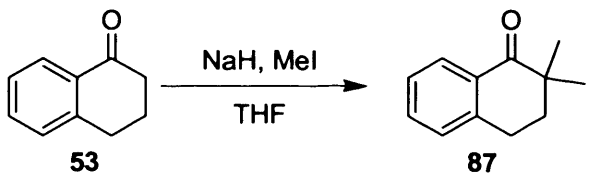


Fig 3.31 Dimethylation of Tetralone

Once again the ketone failed to react in reductive amination reactions and condensation reactions with hydrazine and benzoyl hydrazone. Asymmetric reduction of the ketone with DIP-Cl and enzymatic resolution of the corresponding alcohol **88** with CLEC-PC also failed. The crude mixture from the reaction of the alcohol with sodium azide did contain the characteristic azide peak (2115 cm^{-1}) in the IR spectrum

and the NMR data displayed encouraging signals. However, after purification by column chromatography the product decomposed violently during concentration under vacuum. Attempts were made to reduce the azide **89** directly, without isolation, using lithium hydride or palladium on charcoal and hydrogen but these failed.

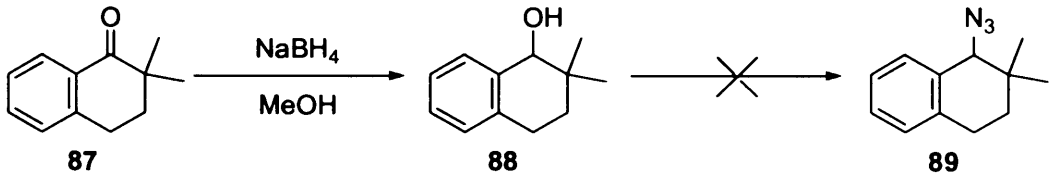


Fig 3.32 Reduction and Attempted Substitution on Dimethyltetralol

3.1.4 Synthesis of Amine on Quaternary Carbon Centres

Again, tetralone was chosen as the starting material for the synthesis of amine **56**. Treatment with methyl magnesium bromide led to formation of 1,2,3,4-tetrahydro-1-methylnaphthalen-1-ol **90**, in 87% yield.[50] However, conditions suitable for substitution of the alcohol (tosylation or mesylation in the presence of sodium azide, treatment with DPPA) invariably lead to internal elimination, yielding 4-methyl-1,2-dihydro-naphthalene **91**. Such activations of alcohols are invariable carried out in the presence of a base. Once the alcohol has been converted into a good leaving group, the two position is immediately deprotonated which leads to the elimination.

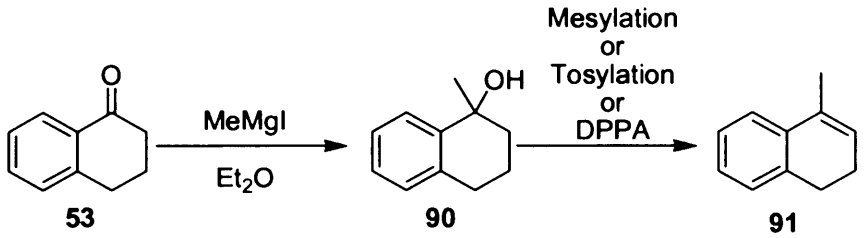


Fig 3.33 Synthesis of **91** and Subsequent Elimination

Another strategy was adopted starting from 1-methylene-1,2,3,4-tetrahydro-naphthalene **92** synthesised from tetralone via a Wittig reaction.[51] In the presence of ICl, the iodonium ion is formed. Subsequent addition of sodium azide lead to the formation of 1-azido-1,2,3,4-tetrahydro-1-(iodomethyl)naphthalene **93** in 73% yield. It was hoped that reduction with lithium aluminium hydride would lead to formation of the corresponding amine, however this molecule could not be isolated as a spontaneous intramolecular nucleophilic attack of the amine on the iodide leads to formation of aziridine **94** in 55% yield.

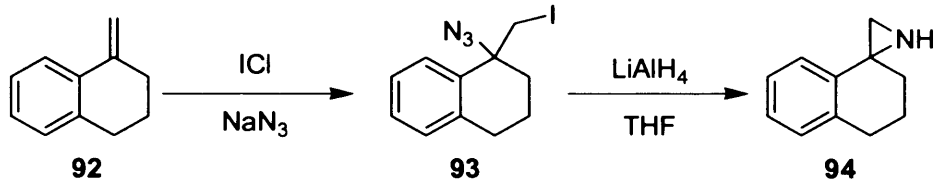


Fig 3.34 Synthesis of Azide **93** and Intramolecular Cyclisation to Yield Aziridine **94**

Opening of the aziridine under basic conditions, which should have yielded the desired product, only led to a complex mixture with no sign of the amine by GC/MS. An acidic opening of this molecule would not be suitable, as literature shows that this would lead to the external amine.[52] Removing the iodine before reducing the azide would prevent the formation of the aziridine, so a radical deiodination of **93** to form azide **95** was carried out.[53] Although one major product was observed it was clearly not the desired azide, as the characteristic peak was not present in the IR spectrum.

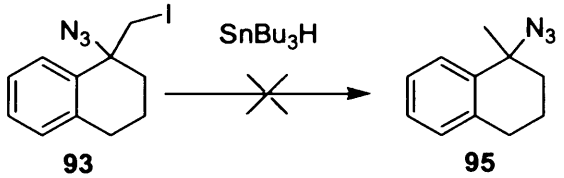


Fig 3.35 Radical Deiodination of **93**

The crude product of the direct addition of azidic acid (HN_3), formed in situ from sodium azide and a solution of HCl in diethyl ether, did appear to contain the azide **95**. However, the product appeared to decompose during purification by column chromatography giving an identical product to that formed during the deiodination reaction. The NMR data appeared to be consistent with 2-methyl-4,5-dihydro-3*H*-benzo[β]azepine **96** and a literature search based on this structure showed that the

rearrangement of the azide to form this product is already documented. In this publication the synthesis of azide **95** from **92** was also attempted using a similar procedure and similar problems were encountered.[54]

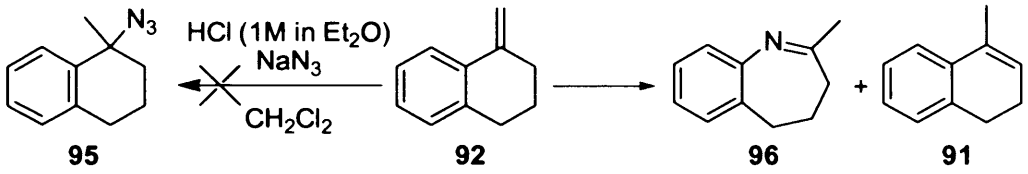


Fig 3.36 Reaction of **85** with Azidic Acid

As the azide is formed as an intermediate, reduction of the crude reaction mixture without further purification was attempted under various conditions, but again only products **96** and **91** could be isolated. This suggests either that the hydrogenation catalysts employed actually catalyses the rearrangement or that the catalyst was poisoned by impurities in the crude product.

A final attempt was made to synthesise **56** via a Ritter reaction. **92** was allowed to reflux in acetonitrile in the presence of HCl (1-10 equivalents).[55] This should have afforded the acetylated amine **97**; however, only a mixture of starting material and **91** was recovered. The failure of **92** to react in the Ritter reaction is probably due to the stability of the intermediate formed after addition of a proton to the double bond due to delocalisation of charge through the aromatic system and the weak nucleophilic properties of acetonitrile. Additionally, the presence of **91** suggests the possibility of an elimination reaction of the intermediate but may be due to the fact that the internal double bond is thermodynamically more favoured and isomerisation occurs at high temperature under reflux.

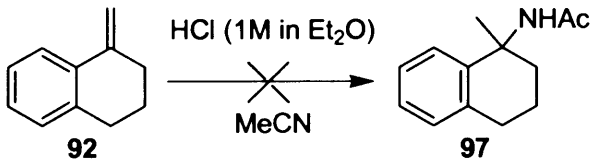


Fig 3.37 Ritter reaction with **92**

In view of the problems encountered in the synthesis of **56,** a different course was followed. Recent work by J. Leighton and co-workers has shown that the synthesis of molecules bearing an amine functionality on a chiral quaternary carbon via the enantioselective allylation of ketone-derived benzoylhydrazones is possible. With this

in mind the benzoylhydrazones of acetophenone **98** and tetralone **99** were synthesized by condensation with benzoylhydrazine.[56]

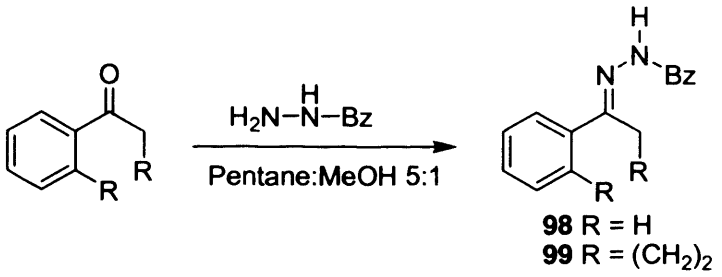


Fig 3.38 Synthesis of Benzoylhydrazones

Allylsilane **100** was prepared, according to the literature procedure, from (*S*,*S*)-pseudoephidrine **101** and allyl trichlorosilane.[56]

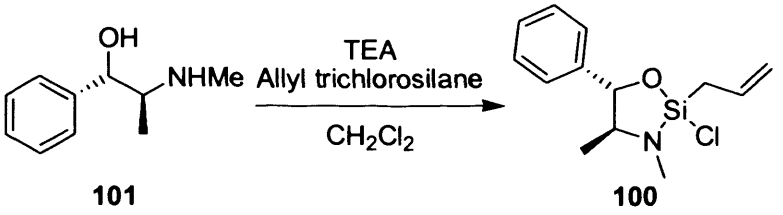


Fig 3.39 Synthesis of the Chiral Allylsilane Reagent **100**

Reagent **100** proved difficult to isolate because it must be first filtered, then concentrated and finally distilled, all under inert atmosphere, as it is extremely air sensitive. Despite several attempts, the product persistently decomposed in the distillation step and was therefore used without further purification. In order to determine the conditions for resolution by chiral HPLC the racemic addition products were synthesized by treatment with allyl trichlorosilane in DMF.[57]

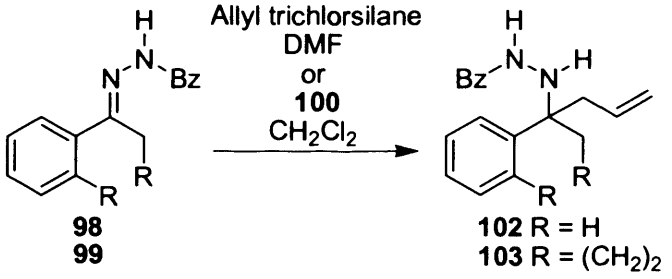


Fig. 3.40 Allylation of **98** and **99**

Unfortunately the products **102** and **103** were only obtained in respectively. The low selectivities are probably due to the presence of residual allyltrichlorosilane from the preparation of reagent **100**. The fact that the molecules contain two nitrogen atoms in

close proximity to the chiral centre, leads to a high level of interaction with the chiral HPLC column and excellent resolution, making them good candidates for separation by preparative HPLC. However, solubility in the solvent systems suitable for the Chiracel-OD preparative column, the only column available to us, was poor and no significant quantities could be resolved by this method.

In order to prepare intermediates for other amines, the benzoylhydrazone of tetralone **99** was treated with different Grignard reagents. Due to the presence of an acidic proton in the substrate, a minimum of two equivalents of reagent were necessary (the first equivalent only serving to deprotonate the substrate). Even with a large excess of Grignard reagent only starting material was recovered. This suggests that, once deprotonated, the substrate becomes deactivated, probably due to delocalisation of charge.

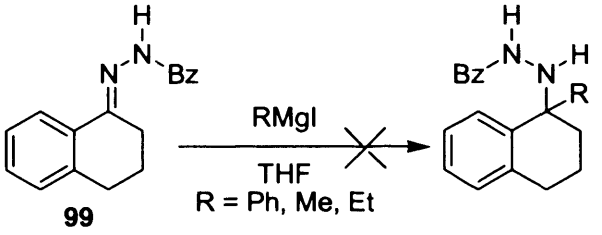


Fig 3.41 Reactions of **99** with Grignard Reagents

3.1.5 Aniline Derivatives

The racemate of 1-(2-amino-phenyl)-ethanol **57** was first synthesised from the reduction of aminoacetophenone with sodium borohydride.

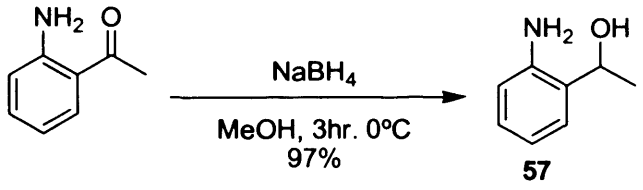


Fig 3.42 Reduction of Aminoacetophenone

As the product contains a free amine, it is unsuitable for resolution by chiral HPLC with the columns available. Attempts to resolve the racemate by chiral GC also proved unsuccessful, as the boiling point of the molecule was too high and the sample decomposed at the high injector temperature. A method had to be found either to reduce the boiling point or to protect the free amine without affecting the chirality of the molecule. 1-(2-Amino-phenyl)-ethanol and other *o*-aminobenzyl alcohols are known to form bicyclic systems know as benzoxazines when allowed to react with aldehydes and ketones.[58] 4-Methyl-1,4-dihydro-2H-benzo[d][1,3]oxazine **104** was therefore synthesised by the addition of formaldehyde to a suspension of racemic 1-(2-amino-phenyl)-ethanol in water. Although the yield was poor and separation of the starting material from the product was difficult, it was possible to resolve this racemate by HPLC.

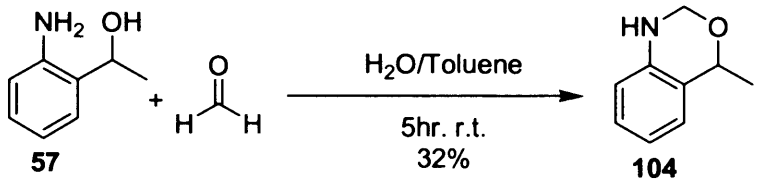


Fig 3.43 Protection of 1-(2-Amino-phenyl)-ethanol as the Benzoxazine

The synthesis of enantiomerically pure 1-(2-amino-phenyl)-ethanol through the selective reduction of aminoacetophenone by DIP-Cl has previously been reported.[59] However, attempts to reproduce this result were unsuccessful.

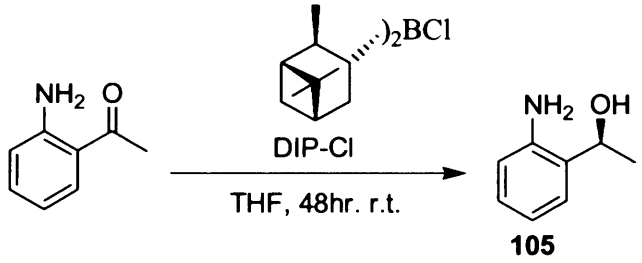


Fig 3.44 Attempted Asymmetric Reduction of Aminoacetophenone

Although the violet and brown intermediates described in the literature are formed, the subsequent workup with alkaline hydrogen peroxide yields no trace of the desired product. An alternative workup with diethanol amine,[59] which is standard for this type of reaction also yielded only starting material. Although the intermediates formed are fully characterised in the publication, the final product is not. α-Pinene, resulting from the decomposition of DIP-Cl has a molecular weight of 136.23, only one mass unit

lower than that of 1-(2-amino-phenyl)-ethanol (137.18). It is possible that the authors mistook the molecular ion of α-pinene for that of deprotonated 1-(2-Amino-phenyl)-ethanol if the reaction was monitored by GC/MS, explaining the high *ee* observed. Acetophenone is volatile and is, therefore, removed along with the solvent during concentration by rotary evaporation, which explains the absence of starting material in the mass spectrum.

Both acetophenone and bromoacetophenone **106** are known to be reduced with high enantioselectivity by DIP-Cl. Introduction of an amine functionality in the *ortho*-position of the corresponding alcohols would provide an alternative route for the synthesis of **105**. 1-Phenylethanol **107** is commercially available and 1-(2-Bromo-phenyl)-ethanol **108** was prepared by reduction of **106** with sodium borohydride.

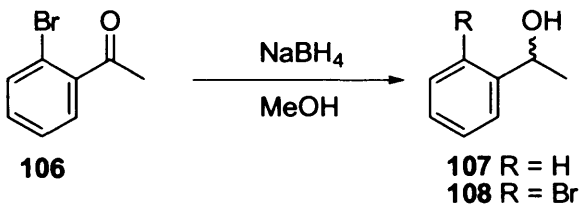


Fig 3.45 Reduction of Bromoacetophenone

1-(2-Bromo-phenyl)-ethanol **108** was employed as the substrate in a Buchwald-Hartwig reaction with benzophenone imine.[60] Alcohol **108** failed to react under the standard conditions for this reaction. This is probably due to presence of an acidic proton in the substrate, which is known interfere with this reaction. An alternative procedure designed for substrates, such as alcohols, containing acidic protons and using LiHMDS as a base, also failed.[61]

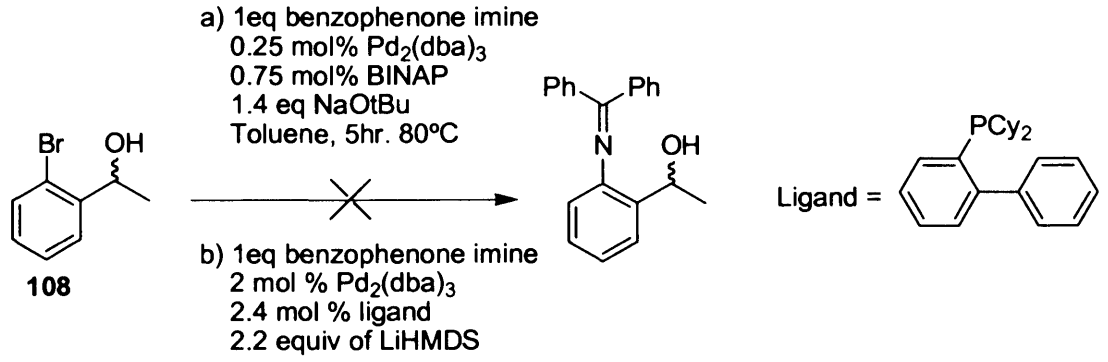


Fig 3.46 Variations on the Buchwald-Hartwig Reaction attempted with **108**

To introduce the amine moiety into alcohol acetophenone, a nitration with HNO_3/H_2SO_4 was carried out.[62] In addition to the introduction of the nitro-group, the alcohol was also oxidised to the ketone resulting in a 1:5 mixture of *ortho-* and *para-*nitrophenyl ethanone **109a/b** in 82% yield.

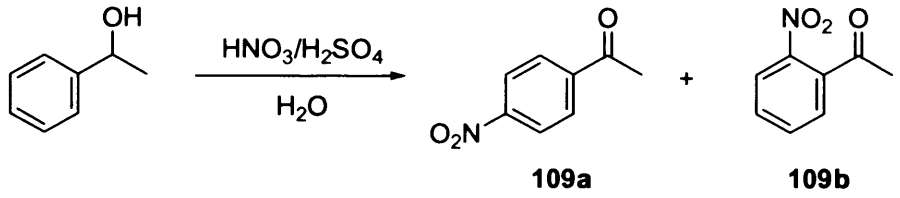


Fig 3.47 Nitration of Acetophenone

Acetophenone was therefore protected as the acetate by reaction with acetyl chloride in acetic anhydride with a catalytic amount of DMAP. Acetate **110** was again treated with a mixture of HNO_3/H_2SO_4. Although the molecule was nitrated, NMR of the crude product indicated a 9:1 preference for the *para*-substituted product **111b**. This reaction was therefore not carried out with the enantiomerically pure alcohol, as the nitrogen was considered to be too far away from the chiral centre.

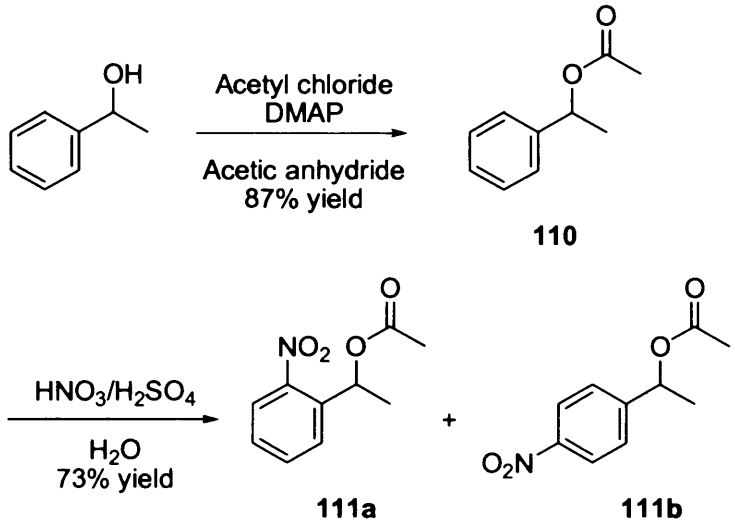
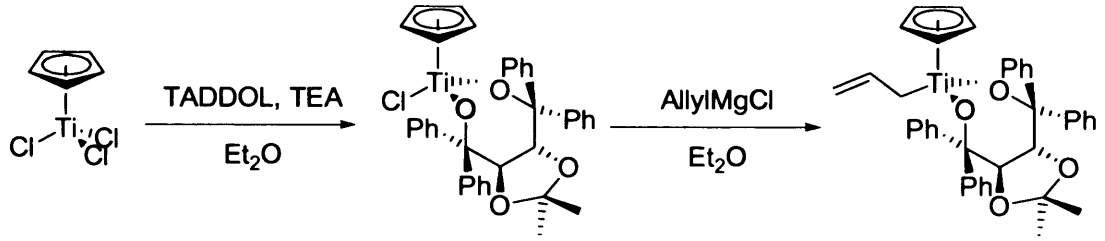


Fig 3.48 Acetylation of 1-Phenylethanol and Subsequent Nitration

The allyl TADDOL titanium complex **112** is often used for the enantioselective addition of allyl groups to aldehydes.[63] This reagent was synthesised from cyclopentadienyl titanium trichloride **113**, which was reacted with TADDOL in the presence of triethyl amine. Intermediate **114** was then treated with allyl Grignard

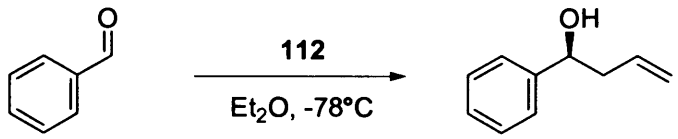
reagent and the precipitate filtered off. The resulting reagent solution was used without further purification.



113 **114** **112**

Fig 3.49 Synthesis of Allyl Taddol Titanium Complex **112**

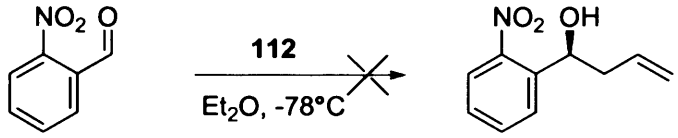
As this reagent is extremely air-sensitive, a test reaction was carried out with benzaldehyde in order to ensure its reactivity and purity. The expected *ee* of 86% was indeed obtained for alcohol **115**.[63]



115

Fig 3.50 Asymmetric Allylation of Benzaldehyde

Disappointingly, the reaction of **112** with commercially available nitrobenzaldehyde **116** failed to yield the desired product. Starting material was also recovered from the reaction of **116** with allyl Grignard, carried out to form the racemate of **117**. It would appear that the presence of the nitro group on the aromatic moiety deactivates the aldehyde, probably due to electronic effects.

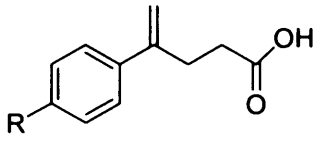


116 **117**

Fig 3.51 Attempted Allylation of Nitrobenzaldehyde **116**

3.2. Substrate Synthesis

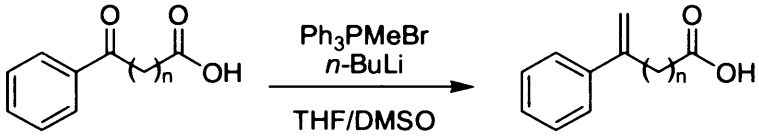
The substrates used in previous investigations have so far all been derivatives of 4-phenyl-4-pentenoic acid **118**.[27] In previous investigations, it has been shown that selectivity is increased when the aromatic moiety bears a strong electron-withdrawing group. The best results to date have been obtained with 4-(4-trifluoromethyl-phenyl)-pent-4-enoic acid **119**.



118 R = H
119 R = CF_3

Fig 3.52 Substrates used in Previous Investigations

Compound **118** was employed as the standard substrate in cyclisation reactions, as it is easily synthesised in good yield from the commercially available 4-oxo-4-phenylbutanoic acid **120** via a Wittig reaction.[64] It was also possible to carry out the same reaction with 5-oxo-5-phenylpentanoic acid **121** to obtain 5-phenylhex-5-enoic acid **122,** which was chosen as a target to investigate the effects of chain-length on enantio- and regioselectivity, this molecule being able to form both five- and six-membered rings.

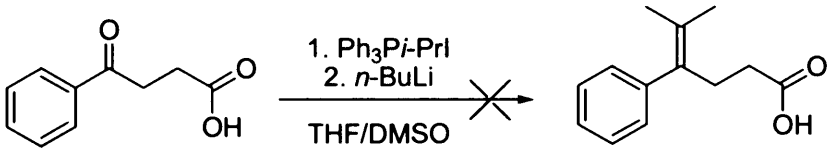


n = 2 **120**
n = 3 **121**

n = 2 **118**
n = 3 **122**

Fig 3.53 Synthesis of **118** and **122**

Attempts were also made to synthesise 5-methyl-4-phenyl-hex-4-enoic acid **123**, chosen as a substrate to investigate the effects on enantioselectivity of steric hindrance in the vicinity of the double bond, via a Wittig reaction using *i*-proyltriphenyl phosphoniumiodide and **124** as a substrate.



124 **123**

Fig 3.54 Wittig Reaction of **124**

As the starting material is an acid, it was first deprotonated by the addition of *t*-BuLi in a 50:50 mixture of dry THF/DMSO and subsequent heating to 60 °C. The failure of this reaction could be due inefficient deprotonation of the acid, the methyl ester was synthesised, as an alternative substrate, by acid catalysed condensation with methanol. Unfortunately this had no significant effect on the Wittig reaction. The colour change generally associated with ylide formation was only observed when using *t*-BuLi at low temperature and vanished after a few minutes, even when using literature procedures, developed for this particular phosphonium salt.[65] This would indicate that the ylide is not formed. A test reaction carried out using benzaldehyde confirmed this, as this substrate also failed to react.

A literature procedure for the synthesis of **124**, using α-isopropylstyrene synthesised from 2-methyl-1-phenylpropan-1-one **125** via a Wittig reaction was then attempted.[66] α-Isopropylstyrene was first brominated in a photochemical reaction. Subsequent treatment with a solution of sodium diethyl malonate lead to the formation of 3-(3-methyl-2-phenylbut-2-enyl)pentanedioic acid **126**, however, pyrolysis of the diacid failed to yield the desired product. Instead of a pale yellow, an insoluble black tar was obtained.

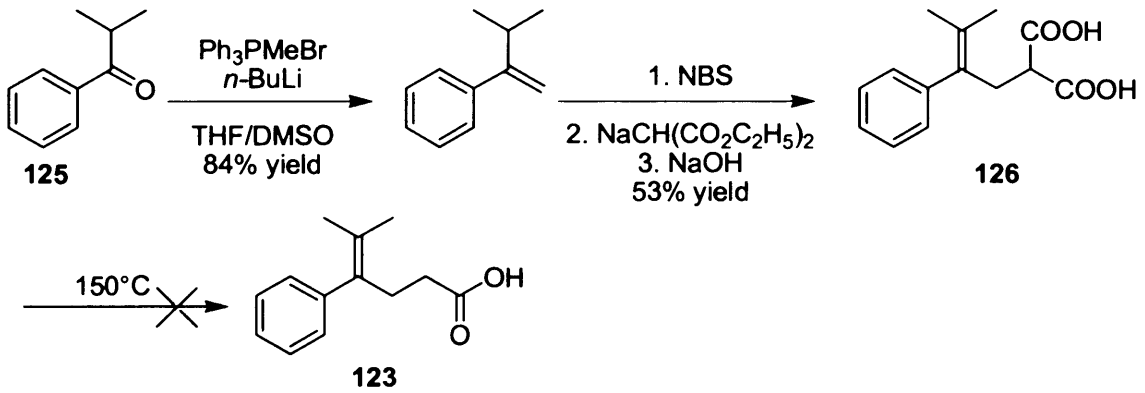


Fig 3.55 Synthesis and Attempted Pyrolysis of Diacid **126**

A new method was developed to synthesise this molecule via a rearrangement reaction. The Grignard from the reaction of α-bromostyrene **127** with magnesium was allowed to react with acetone.[67] The resulting alcohol **128** was treated with trimethyl orthoformate and acetic acid. Under reflux the resulting intermediate **129** underwent a Johnson-Claisen rearrangement yielding the methyl ester **130**, which was then cleaved by treatment with lithium hydroxide to the desired acid **123**.[68]

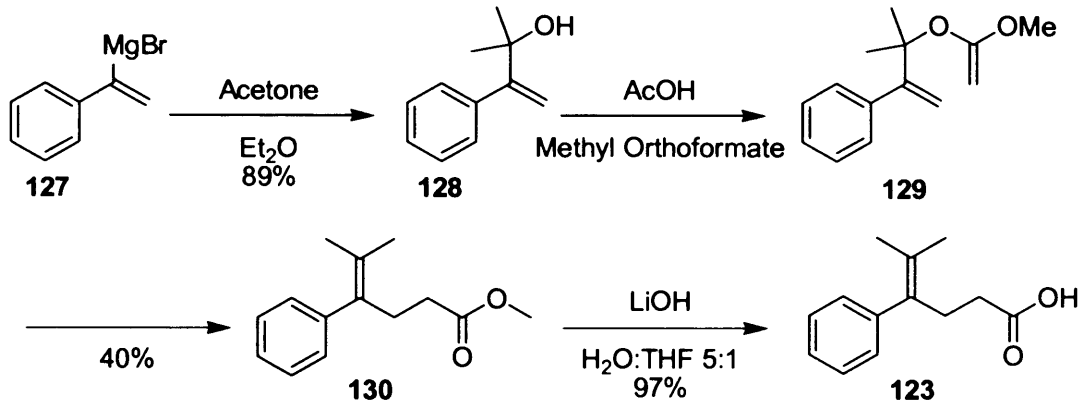


Fig 3.56 Synthesis of **123**

Substrates with internal double bonds were also synthesised. (*E*)-4-Phenylbut-3-enoic acid **131** was synthesised in 66% yield via a literature procedure from malonic acid and phenylacetaldehyde in pyridine.[69]

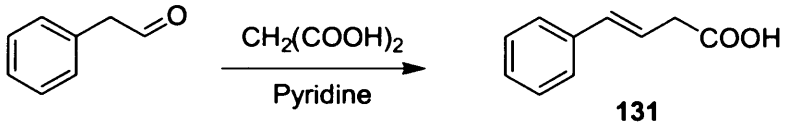


Fig 3.57 Addition of Malonic Acid to Phenylacetaldehyde

Similarly, (*E*)-5-phenylpent-4-enoic acid **132** was synthesised in 63% yield using a procedure treating cinnamyl chloride with malonic acid.[70]

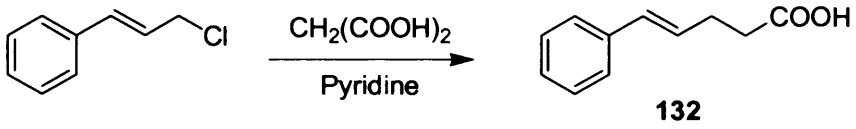


Fig 3.58 Addition of Malonic Acid to Cinnamyl Chloride

4-Bromo-pent-4-enoic acid tert-butyl ester **133** can be used as a precursor for derivatives of 4-phenyl-4-pentenoic acid. It is easily synthesised, according to a literature procedure, from the reaction of tert-butyl acetate with 2,3-dibromopropene in the presence of LDA generated in situ from diisopropylamine and n-butyllithium.[71]

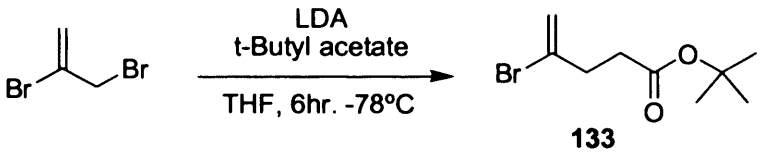


Fig 3.59 Synthesis of 4-Bromopent-4-enoic acid tert-butyl ester **133**

This molecule was then employed in a series of Suzuki Miyaura coupling reactions with 2-furan boronic acid **134** and benzyl 9-BBN **135** (a substitute for benzyl boronic acid, which is known to perform poorly in such reactions).[72]

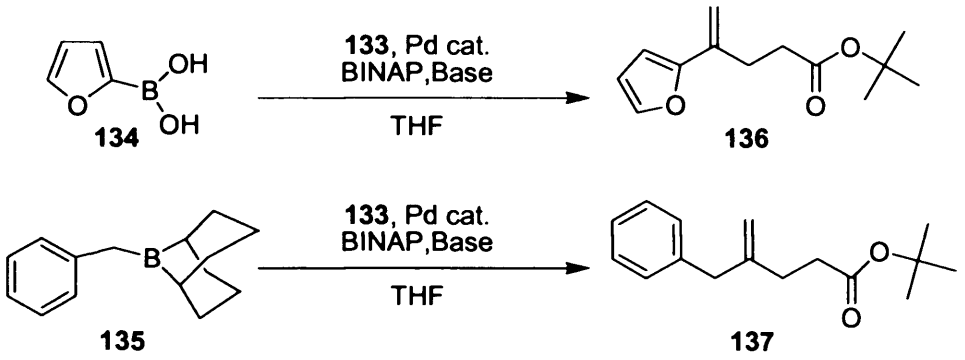


Fig 3.60 Suzuki Miyaura Coupling Reactions with 4-Bromo-pent-4-enoic acid tert-butyl ester **133**

The coupling reactions were carried out under a number of different conditions using different catalysts and bases and the results are shown in table 3.1.

Table 3.3 Results of Suzuki-Miyaura Coupling Reactions

Boronic Acid	**Pd Catalyst**	**Base**	**Yield**
2-Furan boronic Acid	$Pd(PPh_3)_4$	KOH	trace
2-Furan boronic Acid	$Pd(PPh_3)_4$	K_3PO_4	trace
Benzyl 9-BBN	$Pd(PPh_3)_4$	KOH	23%
Benzyl 9-BBN	$Pd(PPh_3)_4$	K_3PO_4	50%
Benzyl 9-BBN	$Pd_2(dba)_3$	K_3PO_4	traces
Benzyl 9-BBN	$Pd(OAc)_2$	K_3PO_4	traces

Although it was possible to obtain product **137** in reasonable yield on a milligram scale, as soon as the reaction was scaled up only traces of product were observed. No trace of product **136** was obtained from the reactions with 2-furan boronic acid. As these reactions were unsuccessful, an alternative procedure was sought. In recent publications, it has been claimed that such coupling reactions can be carried out in aqueous media, without palladium catalysts, using microwave irradiation to promote the reaction.[73] In the same publication, it is also stated that the reaction can be carried

out in a sealed tube by heating to 150°C for 2 hours. In order to ascertain whether or not this procedure is suitable for our substrates, attempts were made to synthesise *t*-butyl-4-phenyl-4-pentenoate **138** from phenyl boronic acid and **133**.

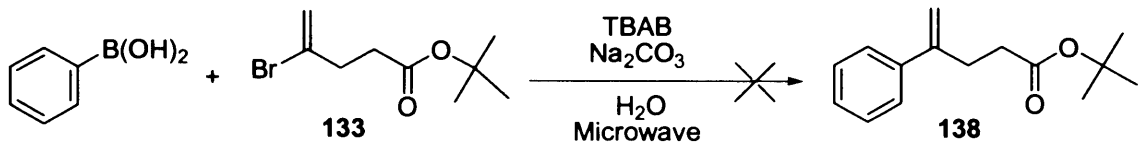


Fig 3.61 Palladium-Free Suzuki Coupling Reactions of **133** with Phenyl Boronic Acid

Despite several attempts under different conditions, no product was obtained. In each reaction, it was possible to recover all starting materials. No product was obtained when heating in a sealed tube and it was not even possible to reproduce the reaction between phenyl boronic acid and 1-(4-bromo-phenyl)-ethanone **139** to give 1-biphenyl-4-yl-ethanone **140** as described by the authors.

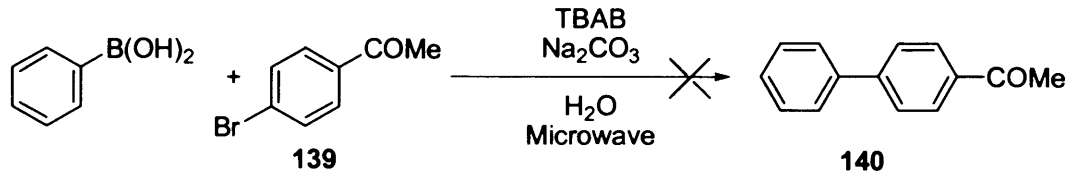


Fig 3.62 Attempt to Reproduce Results Published by Leadbeater *et al.*

Although disappointing, these results were not altogether unexpected, as Leadbeater suggests that some other factor may be involved in the reaction. It has, in fact, been suggested that traces of transition metals, present in the sodium carbonate, catalyse the reaction. Success is therefore dependent on the source of carbonate. In more recent work Leadbeater himself has shown that more consistent results are obtained when a catalytic amount of palladium on activated charcoal is added to the reaction mixture.[74]

Previous studies have shown that terpene alcohols can be stereoselectively cyclised using selenium electrophiles.[75] The molecule shown below is the result of the cyclisation of homogeraniol **141**. These reactions are very useful, as they include the formation of a carbon-carbon bond.

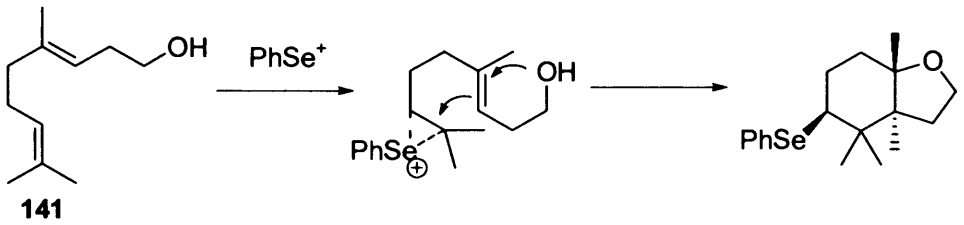


Fig 3.63 Structure Resulting from the Cyclisation of Homogeraniol with Diphenyl Diselenide

It would be interesting to study the use of chiral amine ICl in this reaction to investigate the effects on enantioselectivity. In order to carry out this investigation attempts were made to synthesise homogeraniol from commercially available geraniol **142** using a literature procedure.[75] Geraniol was first oxidised in a Swern oxidation with activated DMSO to yield aldehyde **143**. Treatment of **143** with a methyl phosphorus ylide in a Wittig reaction lead to the formation of (*E*)-4,8-dimethyl-1,3,7-nonatriene **144**. Hydroboration of this molecule should have lead to the formation of homogeraniol.

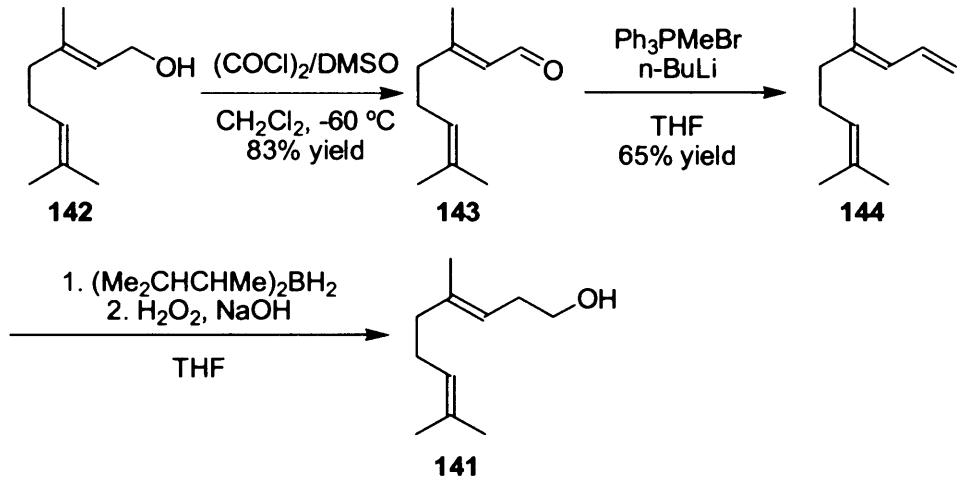


Fig 3.64 Attempted Synthesis of Homogerniol

Neither the desired product nor the starting material could be recovered from the final reaction step. Analysis of the reaction mixture by GC/MS at intervals of 10 minutes showed that trace quantities of homogeraniol were initially present after a short reaction period. However, when the reaction is allowed to proceed for longer than 20 minutes, a number of by products were observed as the starting material was consumed. A decrease in the amount homogeraniol present was also observed indicating that the by-products were due not only to side reactions but also to

decomposition of the product. Even when the reaction was quenched before complete conversion of the starting materials, it was not possible to isolate the desired product.

3.3 Conclusion

The most successful method for the preparation of enantiomericaly pure has been the enzymatic resolution of alcohols followed by introduction of the nitrogen in the form of the azide and subsequent hydrogenation, the procedure used for the preparation of amines **50** and **76**. Direct synthesis of the amines followed by resolution of the enantiomers by formation of diastereoisomers proved problematic, as in many cases it was difficult to remove the chiral auxiliary in order to obtain the free amine. Unfortunately, the enzymatic resolution of alcohols was not appropriate for more hindered systems such as ketones **81** and **87**. In such cases no reaction was observed. The degree of steric hidrance in these systems becomes clear from the failure of subsequent reactions, such as stereoselective reduction with DIP-Cl and attempts to introduce nitrogen into the molecules by nucleophilic substitution with NaN_3 or DPPA, both of which failed.

Attempts to synthesise ligands containing amines on quaternary quaternary centres adjacent to an aromatic moiety, such as amine **56** all failed. The use of tertiary alcohols as intermediates for such molecules proved to be flawed, as activation of the alcohol invariable lead to elimination. Alternative methods for the synthesis of amine **56** via iodoazide **93** or azide **95** also failed. The most promising results in the synthesis of this type of amine were obtained through the addition of Leighton's chiral allylsilane to benzoylhydrazones and more work should be carried out to improve on this reaction and the subsequent cleavage to the free amine.

Chapter 4

Cyclisation Reactions

4.1 Optimisation of the standard cyclisation reaction

As has been previously discussed, reaction conditions for the standard cyclisation reaction of 4-phenyl-pent-4-enoic acid with ICl in the presence of 1,2,3,4-tetrahydronaphthyl-1-amine have previously been optimised with respect to concentrations and the complexation time of ICl to the amine.[27]

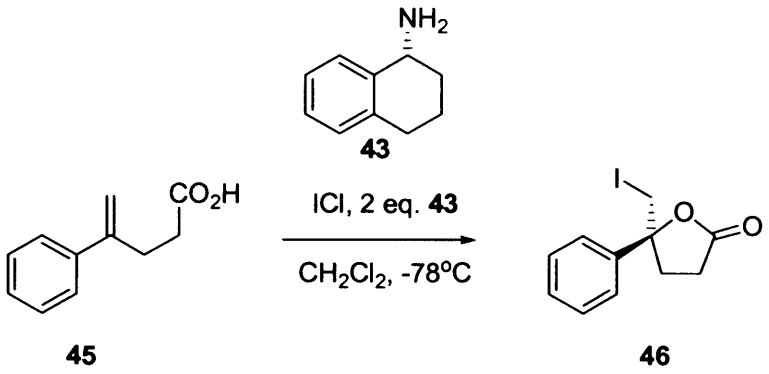


Fig 4.1 Cyclisation of 4-Phenyl-pent-4-enoic **45**

It was found that the amine and ICl must be allowed to stir for 30 min. before cooling to -78°C and addition of the substrate in order to obtain optimum selectivity. However, reproduction of the best results obtained to date proved elusive; results were not at all consistent. After redistillation of the amine and further purification of the substrate and solvents, it was clear that something else must be responsible for the inconsistent results observed. An investigation was therefore carried out, varying the stirring temperature during the 30 min. complexation period of the amine and ICl. Results are shown in the table 4.1.

Table 4.1 Optimisation of temperature during the complexation period of amine **43** and ICl.

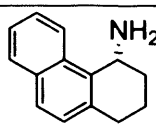
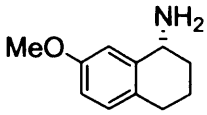
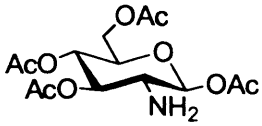
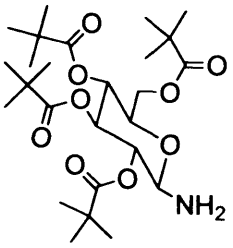
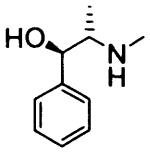
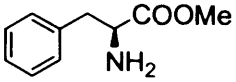
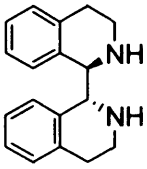
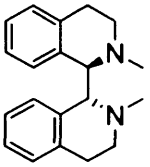
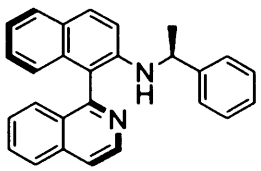
Stirring Temperature (°C)	*ee* (%) of Product (***R***)-**46**
26	33.7
28	36.6
30	40.6
32	45.5
33	46.2, 46.4, 45.9
34	42.3
36	38.1

It can clearly be seen that, with increasing temperature, the enantiomeric excess of the of the product increases, reaches a maximum and then decreases again. The temperature was first increased in 2°C steps and then in 1°C around the temperature, which lead to the highest selectivity. The best result was then repeated in order to prove reproducibility. The stirring temperature during the complexation period appears to be a far more important factor than previously expected. The optimum temperature appears to be 33°C. Subsequent standard cyclisations, carried out with these new optimised parameters, have proved reproducibility well within experimental error. The quality of the ICl solution has also proved to be a significant problem with regards to reproducibility. Once exposed to moisture and/or air ICl decomposes to form HCl and I_2, even trace quantities of which appear to lead to low *ee* in the product. These observations are consistent with computational results (discussed in chapter 6), which show that interactions between the amine and HCl are energetically more favourable than those with ICl. It has not been possible to reliably reproduce results using solutions of ICl, prepared by ourselves, so a commercially available 1M solution of ICl in CH_2Cl_2 was employed in all reactions. Even when stored in a dry Schlenk flask under argon, this solution has a relatively short shelf life. To ensure the quality of the ICl solution, a test cyclisation using 1,2,3,4-tetrahydronaphthyl-1-amine was always carried out in parallel with all cyclisations described below.

4.2 Evaluation of Different Amine Ligands

The amines synthesised have been tested in the standard cyclisation reaction and the results are shown in the table 4.2.

Table 4.2 Results of Reactions Carried out with Chiral amine Ligands

Amine ligand	*ee* (%) of Product **46**
 **76**	19% (S)
 **50**	43% (R)
 **145**	6% (R)
 **146**	12% (R)
 **147**	0%
 **148**	0%
 **149**	27% (R)
 **150**	No Reaction
 **151**	22% (S)

Amine **76** leads to a disappointingly low *ee*. The substituted tetrahydronaphthylamine **50** produces a relatively high *ee* but still lower than the best result recorded so far with 1,2,3,4-tetrahydronaphthyl-1-amine. This suggests that substituents and variations on the aromatic moiety of the molecule have no positive effect on stereoselectivity.

Sugars provide a readily available and cheap source of chirality. With this in mind two glucose amine derivatives, the acetyl protected **145** and the pivaloyl protected **146** derivatives were employed as chiral amine ligands. These two molecules differ only in the protecting groups but the pivaloyl moiety is much bulkier than the acetate. Tetra-*O*-acetyl glucosamine **145** showed little selectivity. The more hindered pivaloyl protected glucose derivative **146** performed slightly better, as expected, but neither result was encouraging enough to continue along this path.

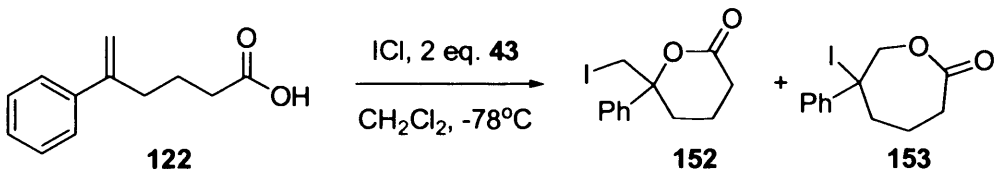
Again, ephedrine **147** is a readily available natural product and was chosen as a ligand because only α-amino alcohols have so far been tested in this reaction. The methyl ester of phenyl alanine **148** was chosen, as no amino ester have been tested to date. α-Amino alcohols had already been shown to perform poorly in this reaction. As expected the reaction catalysed by phenylalanine methyl ester showed no selectivity, as was the case with the corresponding alcohol.[27]

149 and **150**, biisoquinoline derived chiral amines provided by M. Elliott's research[76] group were chosen, as only very few ligands with axial chirality have been tested so far. The bidentate amine ligands provided an interesting result. Compound **149** resulted in relatively low enantiomeric excess but no reaction is observed when **150** is employed. This implies that the latter binds the iodine too strongly for any reaction to occur. As these amines are so similar in structure, it may be possible to tune the electronics of the system by including different substituents and thereby optimising the reaction. In both cases, the same results were observed whether one or two equivalents of amine were employed.

Finally, chiral amine **151** provided by J. N. Johnston was tested.[77] This molecule is of interest because it possesses both axial chirality and a chiral centre adjacent to the amine functionality. Furthermore, two different nitrogen functionalities are present, a secondary amine and a nitrogen in the heterocyclic system. Again, the same results were observed whether one or two equivalents of amine were employed.

4.3 Substrate Cyclisations

The substrates synthesised were first cyclised with ICl in CH_2Cl_2 at room temperature in order to obtain the racemates for HPLC analysis. Cyclisations were then carried out with 1,2,3,4-tetrahydronaphthyl-1-amine and ICl according to the standard procedure developed. Cyclisation of **122** leads to a mixture of two products as shown in figure 4.1. NMR data and the two carbonyl frequencies at ν = 1732 cm^{-1} and 1759 cm^{-1} in the IR spectrum suggest that both the six and the seven-membered lactones have been formed (carbonyl frequencies for unsubstituted six and the seven-membered lactones are ν = 1727 cm^{-1} and 1750 cm^{-1}).[78] It was not possible, however, to separate the two products. As reactions with the chiral amine-ICl complex are carried out at -78°C, the thermodynamically more stable structure should be favoured. Baldwin's rules do not help to predict which might be the major product in this case, as both 7-*endo-trig* and 6-*exo-trig* cyclisations are favourable. Analysis by HPLC and using a diode array detector showed two sets of enantiomers in a 3:1 ratio both with identical *ee* of 39%. NMR suggests that the major component is the six-membered ring **152**, however, evidence of decomposition on the column was observed and two dimensional TLC also showed evidence of decomposition. This may well be due to elimination of HI from the seven-membered lactone **153**.

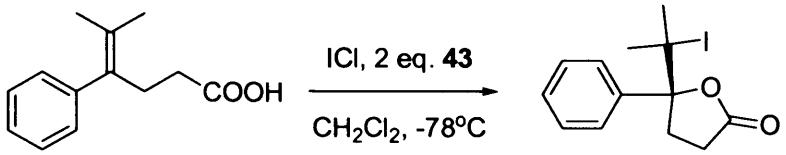


122 **152** **153**

Fig 4.1 Cyclisation of **122** under Standard Conditions

Cyclisation of **123** to yield lactone **154** also proved difficult to work-up and purify. Again, elimination of the iodine is possible in this product and occurred readily, as was apparent from the deep purple colour observed on the silica during column chromatography. Decomposition was also observed when the compound was dissolved in $CDCl_3$ for NMR analysis. It was possible, however, to isolate the product by column chromatography on alumina and NMR data was collected after neutralization of the deuterated solvent. The product proved too unstable for analysis by mass spectrometry, as it decomposed within a few hours, even when stored below 0°C. It had been hoped that a more highly substituted double bond would slow down

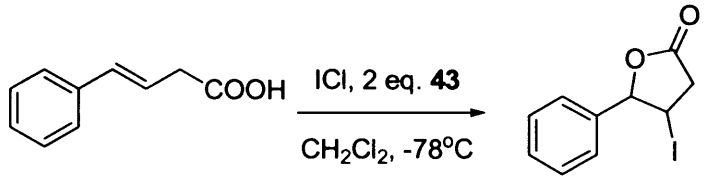
the reaction causing an increase in *ee*. This is not the case, however, and an enantiomeric excess of 45% was observed.



123 **154**

Fig 4.2 Cyclisation of **123** Under Standard Conditions

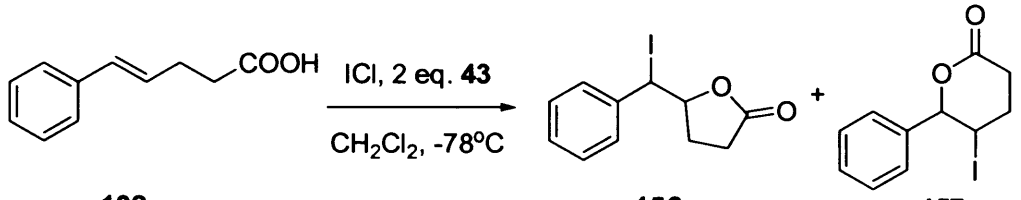
The product from the cyclisation of **131** was more easily purified, but could not be resolved using the chiral HPLC columns available. Attempts to analyse **155** by chiral GC also failed, due to decomposition of the product.



131 **155**

Fig 4.3 Cyclisation of **131** under Standard Conditions

Compound **132** again cyclises to form two different products. In this case it was possible to isolate and identify the two isomers. Compounds **156** and **157** were formed in a 7:3 (isolated yields of 64% and 27%) ratio and in 43% and 42% *ee*, respectively.



132 **156** **157**

Fig 4.4 Cyclisation of **132** under Standard Conditions

This result is significant, as it demonstrates that this method of reagent-controlled iodolactonisation can be employed for the selective cyclisation of compounds containing *trans* disubstituted double bonds, a group of compounds not previously investigated.

4.4 Conclusions

It has so far not been possible to obtain reproducible results using the previously optimised reaction conditions for the standard cyclisation of 4-phenyl-pent-4-enoic acid with ICl in the presence of 1,2,3,4-tetrahydronaphthyl-1-amine. This problem has been overcome by optimising the stirring temperature during the 30 min. complexation period of the amine and ICl, a parameter which had previously not been taken into account. The results show that varying the temperature during the complexation period leads to considerable fluctuations in enantiomeric excess in the product (33-46% *ee*). It has been shown that it is possible to obtain reproducible results by maintaining a steady temperature during the complexation period. The best results were obtained by stirring the mixture of amine and ICl at 33°C over ½ an hour. An *ee* of 46% was observed with a variation of ± 0.5%, well within experimental error.

The results from the cyclisation reactions carried out with amines **76** and **50** suggest that substituents and variations on the aromatic moiety of the molecule have no positive effect on stereoselectivity. The two glucose amine derivatives, **145** and **146** derivatives showed little selectivity. Even though the more hindered pivaloyl protected glucose derivative **146** performs slightly better, neither result is encouraging enough to continue along this path. The reactions carried out in the presence of ephedrine **147** and the methyl ester of phenylalanine **148** both lead to isolation of the racemic lactone. This was no real surprise as previous investigations have shown that amino acids and amino alcohols ligands lead to little or no selectivity.[27] Compound **149** results in relatively low enantiomeric excess but no reaction is observed when **150** is employed. This implies that the latter binds the iodine too strongly for any reaction to occur. As these amines are so similar in structure, it may be possible to tune the electronics of the system by including different substituents and thereby optimise the reaction. In both cases, the same results are observed whether one or two equivalents of amine are employed. Amine **151** only leads to a low selectivity. Again, the same results are observed whether one or two equivalents of amine were employed. This suggests that in the case off diamines only one equivalent of amine is necessary. None of the new ligands tested performed better than 1,2,3,4-tetrahydronaphthyl-1-amine, which has been shown to be the best lingand for this reaction in previous investigations.[27]

The cyclisation of substrate **122** shows that little regioselectivity is observed when more than one product is possible in the reaction. The stereoselectivities are also lower than those observed with the standard substrate 4-phenyl-pent-4-enoic acid. The low selectivities observed in the cyclisation of substrate **123** show that steric hindrance around the double bond of the substrate dose not lead to higher selectivity by slowing down the reaction. This suggests that other factors, such as interactions between the ligand and the substrate are more important for the transfer of chirality than the speed of the reaction. Although the cyclisations of substrates **131** and **132** lead to lower selectivities than those observed with 4-phenyl-pent-4-enoic acid, they do demonstrate that this reaction can also be carried out using substrates which contain *trans*-disubstituted double bonds.

Chapter 5

Alternative ligands and electrophiles

5.1 Silver Cyclisations

The use of silver as a catalyst for cyclisation is well documented.[79] As Ag^+ is less reactive than I^+, the use of silver in lactonisation reactions may lead to higher stereoselectivities when used in combination with chiral ligands. A series of silver salts were tested in cyclisation reactions with our standard substrate.

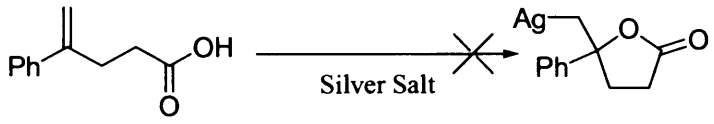
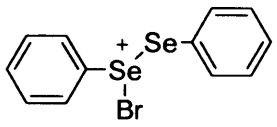


Fig 5.1 Proposed Silver Cyclisationof Standard Substrate

Silver nitrate, carbonate and triflate were tested in solvents such as CH_2Cl_2, THF and methanol and mixtures of these solvents with water. Unfortunately none of the reactions yielded any cyclised product and the starting material was recovered in all cases. This is possibly due to the fact that our substrate is more sterically hindered than those seen in the literature. Examples of silver mediated cyclisations are also more common for substrates where nitrogen, rather than oxygen, is the heteroatom in the nucleophile.[79] Different solvent systems were used because of solubility issues. Only a 1:1 mixture of THF:water could dissolve both the silver salts and the substrate.

5.2 Chiral Diselenide Ligands

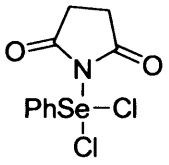
In a recent publication Tunge and coworkers showed that diphenyl diselenide catalyses the halolactonization of unsaturated acids with *N*-halosuccinimides under mild conditions.[80] A catalytic cycle is suggested, where the halide is first transferred to the diselenide forming an intermediate **158** in which the halide binds to one selenium atoms.



158

Fig 5.2 Proposed Structure of Intermediate

Tunge has also reported on the use of phenylselenenyl chloride in combination with *N*-chlorosuccinimide for the α-chlorination of ketones[81] and the regioselective chlorination of olefins.[82] Here, it was possible to isolate an intermediate **159** formed from the oxidative addition of *N*-chlorosuccinimide to PhSeCl.



159

Fig 5.3 Intermediate **159,** formed by Addition of *N*-Chlorosuccinimide to PhSeCl.

Whether the first suggested intermediate is present, or traces of halide ions from the *N*-halosuccinimides first cleave the diselenide, leading to the formation of intermediates of the second type, it is possible that, if chiral diselenides are employed in such reactions, stereoselectivity may be observed. In order to ascertain whether or not these conditions were suitable for the standard lactonisation reaction, a test cyclisation was carried out using the standard substrate with NBS and a catalytic amount of diphenyl diselenide.

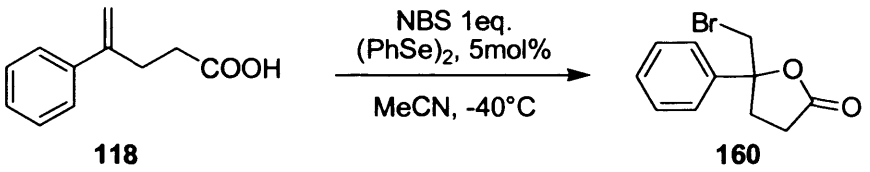


Fig 5.4 Cyclisation of the Standard Substrate with NBS and $(PhSe)_2$

As the bromolactone **160** was obtained in good yield, chiral diselenides previously synthesised by Wirth and coworkers were prepared.[83] Bromoacetophenone **106** was first reduced with DIP-Cl to obtain chiral 1-(2-bromophenyl)ethanol **161**. A lithium-halogen exchange, carried out by treatment with *n*-BuLi followed by reaction with elemental selenium, led to the formation of chiral diselenide **162**. The same series of reactions was also carried out with 1-(2-bromophenyl)propan-1-one **163** to yield first 1-(2-bromophenyl)propanol **164** and then ethyl substituted diselenide **165**.

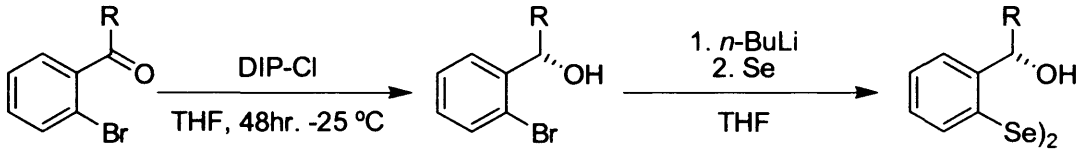


Fig 5.5 Synthesis of Chiral Diselenides

These chiral diselenides were then employed for the cyclisation of the standard substrate using either NIS or NBS as a source of halide. The reactions were carried out at low temperature in a range of solvents and results are shown in table 5.1.

Table 5.1 Cyclisation of the Standard Substrate with Chiral Diselenides and NIS and NBS

Diselenide	Halide Source	Solvent	T/°C	*ee* (%) of Product
162	NIS	MeCN	-40°C	0% (**46**)
162	NBS	MeCN	-40°C	5% (**(*R*)-160**)
165	NIS	MeCN	-40°C	0% (**46**)
165	NBS	MeCN	-40°C	12% (**(*R*)-160**)
165	NBS	C_6H_5Me	-90°C	8% (**(*R*)-160**)
165	NBS	CH_2Cl_2	-78°C	0% (**160**)

Yields in these reactions were close to quantitative, but the enantiomeric excesses obtained were relatively low. Previous studies[84] have shown that the existence of a 1,3 relationship between selenium and the heteroatom on the chiral centre is essential for the transfer of chirality when selenium electrophiles are employed. The interaction between the σ^* orbital of the selenium and the lone pair of the heteroatom leads to a fixed comformation and formation of a pseudo hypervalent selenium species. If such a fixed conformation is not present, low selectivities are observed. If an intermediate similar to **159** is formed via cleavage of the chiral diselenide by trace quantities of halide ions in the succinamide, no such coordination is possible, as no free coordination site is available on the selenium. This would explain the low selectivities observed. Furthermore, when the reaction was carried out in CH_2Cl_2 or with stoichiometric quantities of diselenide, traces of what would appear to be the selenide addition product were observed. This again suggests cleavage of the diselenide. The selectivities observed are probably due more to interactions between the bromine and the alcohol than to interactions with the selenium.

5.3 Phosphine Ligands

There is some evidence[85] that iodine coordinates well to phosphorus, test reactions were therefore carried out using both triphenylphosphine and racemic BINAP in combination with iodine, NIS and ICl. Under standard reaction conditions at low temperature, in CH_2Cl_2 and under argon atmosphere no reaction was observed. However, when the reaction mixture is left open to air overnight at room temperature, cyclisation does occur. It is evident from the colour change when a source of iodine is added to a solution of phosphine, that a reaction takes place.

The reaction mixtures were therefore studied by ^{31}P NMR. Triphenylphosphine displays a peak at –5.9 ppm. When a source of iodine is added, the peak shifts to 66.52 ppm, irrespective of the source and the ratio (measurements were taken with iodine, NIS and ICl in ratios of 1:2, 1:1 and 2:1). Analysis of the reaction, which had been left open to air, showed a peak at 29.2 ppm, confirming the presence of triphenylphosphine oxide.[86] This indicates that an initial complexation takes place

between phosphorus and iodine followed by a slow oxidation. In order to investigate whether or not the iodine is still partially bound to the phosphorus during the oxidation process, the reaction was carried out with chiral BINAP. Unfortunately no selectivity was observed.

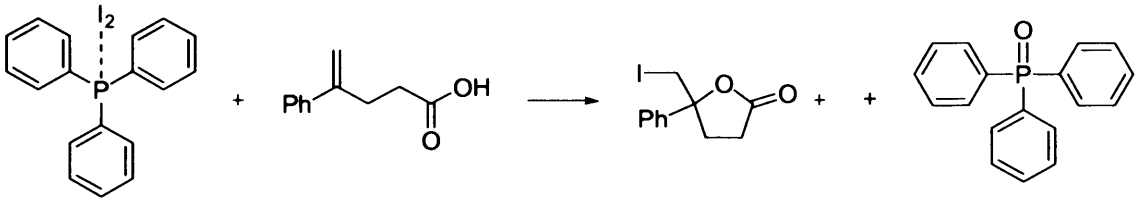


Fig. 5.6 Iodolactonisation in the Presence of Triphenyl Phosphine

5.4 Conclusions

The failure of the silver cyclisations is probably due to the fact that the standard substrate is more sterically hindered than those seen in the literature. Examples of silver mediated cyclisations are also more common for substrates where nitrogen, rather than oxygen, is the heteroatom in the nucleophile.[79]

As it has been shown[84] previous, a 1,3 relationship between selenium and the heteroatom on the chiral centre is essential for the formation of a pseudo hypervalent selenium species necessary to achieve selectivity when chiral selenium electrophiles are employed. If an intermediate similar to **159** is formed via cleavage of the chiral diselenide by trace quantities of halide ions in the succinamide, no such coordination is possible. This would explain the low selectivities observed. Furthermore, when the reaction was carried out in CH_2Cl_2 or with stoichiometric quantities of diselenide, traces of what would appear to be the selenide addition product were observed suggesting cleavage of the diselenide. The selectivities observed are probably due more to interactions between the bromine and the alcohol than to interactions with the selenium.

The ^{31}P NMR from the reactions carried out with phosphorous ligands, clearly shows that initial complexation takes place. However, in the absence of oxygen, the

phosphine-ICl complex appears to be stable and no reaction is observed. Cyclisation only occurs when the reaction is left open to air. NMR analysis shows that the phosphorous atom is oxidised releasing the I^+ ion. The fact that the reaction carried out under aerobic condition with chiral BINAP leads to formation of the racemate proves that the iodine is not partially bound to the phosphorus during the oxidation process and that chiral phosphorous ligands are not suitable for this reaction.

Chapter 6

Computational Results and Discussion

Due to the size of the molecules of interest in this reaction the use of electron-correlated methods such as Møller-Plesset perturbation theory were rejected in favour of less computationally expensive density functional methods. However, some MP2 calculations on model complexes are included for calibration purposes. The choice of basis set also posed a problem. Iodine is not included in most basis sets due to the large number of basis functions necessary to characterise its orbitals, therefore an alternative had to be found. Most calculations that follow were carried out using GAUSSIAN 98,[87] although initial structures for transition states were approximated using the reaction map option in Hyperchem. This is a linear synchronous transit method, which first calculates the best overlap between optimised structures of reactants and products and then averages the structures in order to predict the transition state.[88] These preliminary structures were first optimised using the AM1[89] semi-empirical method, substituting bromine for iodine, as AM1 does not include parameters for iodine. Final calculations were carried out using DFT methods in GAUSSIAN 98.

6.1 Density Functional methods

The underlying principle of density functional theory (DFT) is the assumption that a relationship exists between the total electronic energy and the overall electronic density of a system. If this is the case, knowledge of the electronic density is sufficient to calculate all the properties of the system. This idea was first put forward in the Thomas-Fermi model,[90] which was developed in the nineteen-twenties, but it was not until 1964 that Hohenberg and Kohn were able to prove that ground state energies and other properties could be uniquely defined as the functionals of electron density.[91] This was achieved by means of a *reductio ad absurdum* method disproving

the initial assumption that different external potentials could lead to the same electron density.

The original Thomas-Fermi model was rejected at first due to the fact that the approximation was unable to produce sufficiently accurate results. However, in the last decade the theory has been improved to take more accurate account of effects such as electron correlation and thereby produce highly accurate data at less computational cost than methods such as Møller-Plesset perturbation calculations. This makes it possible to carry out calculations on far larger molecules than is possible with other methods and greatly reduces the time required for calculations on smaller molecules.[92]

As the exact exchange-correlation energy functional (the difference between total energy and the sum of potential, kinetic and electrostatic energy) is not yet known, it is necessary to use an approximation. This is achieved using of Kohn-Sham (KS) theory. KS orbitals, which differ from other kinds of orbitals in that the sum of squares of occupied KS orbitals, give the exact electron density of the system, if the exact exchange-correlation functional was used, are employed in these calculations.[93] In local density approximation, it is assumed that electron density can be treated locally as a uniform electron gas: that is to say, the density is a slowly varying function. Local density approximation generally underestimates exchange energies, creating errors greater than the electron correlation energy. Moreover, the electron-correlation energy itself is also overestimated and, as a result, so are bond strengths. Despite its simplicity and failings this method tends to yield results similar in quality to those obtained by wave mechanics Hartree-Fock calculations. This method was improved by Vosko, Wilk and Nusair (VWN) in 1980 to the local spin density approximation (LSDA) which, in common with all unrestricted methods, treats α and β electron densities separately.[94] The two are therefore equivalent for closed shell calculations but differ for open shell systems. Local density approximation methods can be further improved by considering a non-uniform electron gas. This is achieved by making the exchange and correlation energies dependent not only on electron density but also on its first derivative. Such methods are referred to as gradient corrected approximations (GGA) or non-local methods.

The best results are generally obtained from calculations using hybrid or adiabatically-connected models. These models are linear combinations of functionals

multiplied by coefficients. B3LYP,[95] the method used here is a combination of Becke's three parameter functional and the Lee, Yang, Parr (LYP) correlation functional,[96] which takes the form:

$$aE_X^{Slater} + (1-a)E_X^{HF} + b\Delta E_X^{Becke88} + E_C^{VWN} + c\Delta E_C^{non-local}$$

Equ 6.1 Becke's three parameter functional

The values of the coefficients a, b and c were optimised using the 56 ground state atomisation energies, 42 ionisation potentials, 8 proton affinities and 10 first-row atomic energies of the G1 molecule set.[97] This set of organic molecules, first used for the parameterisation of various methods, was first introduced by the authors of GAUSSIAN. These parameters are: a = 0.8; b = 0.72; c=0.81. The LYP term contains both local and non-local correlation so the correlation term actually used is:

$$(1\text{-c})E_C^{VWN} + c\Delta E_C^{non-local}$$

Equ 6.2 True correlation term in B3LYP

The VWN term, therefore, essentially provides excess correlation as it is more or less equivalent to the local correlation provided by LYP. The B3PW91, which is also used, is identical with B3LYP except that the non-local correlation is provided by the Perdew-Wang 1991 correlation functional.[98]

6.2 Continuum Solvation Models

The basic idea behind continuum solvation theory is to include solvation effects by treating the solvent as a continuum.[99] The solvent is regarded as a uniform polarisable medium characterised by a scalar dielectric constant (ε) into which the solute is placed in a suitable cavity.[100] The creation of the cavity requires energy and is therefore destabilising. If this is added to the dispersion interactions between the solvent and the solute (which are roughly equivalent to the van der Waals energy between the two) and electrostatic stabilisation due to dipole induced-dipole interactions it is possible to calculate the free energy of solvation. This approach is known as the Self-Consistent Reaction Field (SCRF) model. SCRF methods differ in: how the size and shape of the cavity is defined; how the dispersion contributions and charge distributions on the

solute are calculated; how the dielectric medium is described and whether the solute is described classically by a force field; or quantum mechanically by *ab initio* calculations.

An important consideration is the size and shape of the cavity used. Early models used simple shapes such as spheres[101] and ellipsoids of the same volume as that occupied by the solute molecule.[102] This is advantageous as it makes it possible to calculate interactions between the solvent and the solute analytically. This rather crude system can be improved by means of combinations of cylinders and spheres, which more accurately describe not only the volume, but also the shape of the solute molecule. This can be further improved upon by the use of interlocking spheres. Choosing spheres of a suitable size (usually 1.2 times the van der Waals radius of each atom) defines a van der Waals surface. This surface will invariably contain pockets, that are too small to admit solvent molecules. By rolling a ball of approximately the same radius as the solvent molecule across the van der Waals surface one can more accurately define the actual volume taken up by the solute in the solvent. The resulting cavity is known as the solvent accessible surface (SAS). However the difference between the SAS and the van der Waals surface is generally very small and cannot justify the high computational demand involved. The model used here is the Polarisable Continuum Model (PCM), which employs a van der Waals surface type cavity, a detailed description of the electrostatic potential and parameterises the cavity/dispersion contributions based on the surface area.[103]

This method is limited in its representation of interaction of the solvent with the solute in the cybotactic region, the first solvation shell. Effects of the presence of the solute on the bulk or continuum will be shielded by the formation of hydrogen bonds and preferential orientation of the solvent in close proximity to the solute. If the local electric field in the vicinity of the solvent is very high the assumption of a linear response of the solvent will break down and the dielectric response will be over-estimated. As a result, the dielectric constant changes specific to any point in space in the vicinity of the solute. The question then arises as to where the solute stops and the continuum begins.

Although the inclusion of more than one or two explicit solvent molecules treated at the same level of accuracy as the solute is impracticable in the time scale given, one or two solvent molecules will already go a long way towards including first solvation

shell effects. In fact, many first solvation shell data can be gathered from calculations carried out on such clusters without the presence of the continuum.

6.3 Basis Set Modification and Evaluation

Molecules containing heavy elements, from the third row of the periodic table, or lower, pose a great problem in modelling, as they contain a large number of core electrons, which, although unimportant in a chemical sense, must be characterised using a large number of basis functions in order to properly describe the valence orbitals. This problem can be overcome by the use of effective core potentials (ECP). These are functions, which model the core electrons, preventing the valence electrons from collapsing into the core.[104] The valence electrons are then treated explicitly yielding results comparable in quality to all-electron calculations at a fraction of the computational cost. In order to design an ECP a good quality all-electron wave function must first be generated. This is usually achieved using a numerical Hartree-Fock or a relativistic Dirac-Hartree-Fock calculation. The valance orbitals are then replaced by pseudo orbitals, which are designed to behave correctly on the outer part but lack the nodal structure in the core region that is observed in regular orbitals. Finally, the core electrons are replaced by a potential that is so designed that the solutions of the Schrödinger equation produces valence orbitals, that match the pseudo orbitals. These potentials effectively include relativistic effects, which mainly affect core electrons.

The SDD, used for iodine in the calculations that follow, employs the Dunning/Huzinaga full double zeta basis set on the first row and Stuttgart/Dresden ECP's on the remainder of the periodic table. The 46 electron (krypton) core of iodine is described using an ECP.[105] The two 5s-electrons are described at a double zeta level and all 5p-electrons at a triple zeta level. To improve results in the following calculations, a set of d-orbitals, optimised in the ICl-ethene complex, was added. The exponent of the d-type Gaussian function was varied in a series of single point MP2 calculations on ICl with simultaneous geometry optimisation. A cubic fit to the data yielded an optimum value of the exponent (see below). A further shell of sp diffuse functions was added in order to better describe long-range effects, important in

complexation (e.g. polarisability). The exponent for these was estimated by extrapolating beyond the values for the 6-31+G diffuse functions in halogens up to bromine.[106]

Table 6.1 Data for Optimisation of Exponent

Exponent	Energy (a.u.)
0.15	-471.57067
0.2	-471.57327
0.25	-471.57367
0.3	-471.57276
0.35	-471.57129

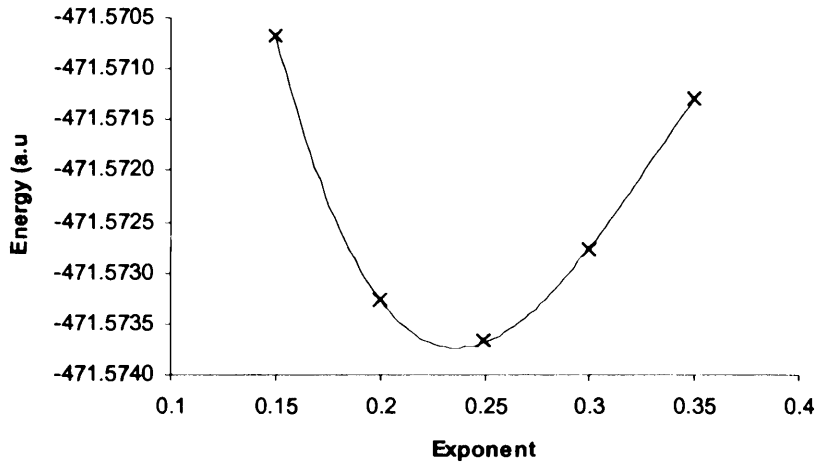
A cubic fit of energy plotted against exponent leads to the following function:

$$f(x) = -1.09x^3 + 1.08779x^2 - 0.331693x - 471.542$$

Equ 6.3 Cubic Fit of Data

Differentiation shows that an exponent of $\alpha = 0.237$ gives a minimum in energy.

Graph 6.1 Overlap of Plot of Energy Against Exponent α with Cubic Fit



For the sake of accuracy all other elements were treated at a higher level of theory. The 6-31+G** basis set was used with polarised and diffuse functions for the same reasons as mentioned above.

A set of preliminary calculations was carried out to compare the results obtained from calculations performed using the modified basis set with B3LYP, B3PW91 and MP2 methods, with experimental results. Experimental data were obtained from a study carried out by Legon[107] on a series of interactions between iodine monochloride and simple Lewis bases. This data was obtained using rotational spectroscopy. Comparison of results was restricted to interactions between ICl and nitrogen and ICl and unsaturated carbon atoms and both of these interactions are relevant to this study. Nitrogen-iodine interactions are important for the formation of the reactive species where both complexation and transfer must be investigated. Interactions between iodine and double bonds are of interest for the investigation of the addition to the double bond in lactonization reactions. Results obtained using the LANL2DZ basis set in combination with B3LYP are also included.

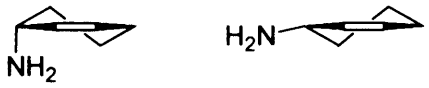
Table 6.2 Comparison of Experimental and Calculated X – ICl Bond Lengths in Å

	Expt.[107]	B3LYP/ SDD(p,d)	B3PW91/ SDD(p,d)	MP2/ SDD(p,d)	B3LYP/ LANL2DZ
N_2 • ICl	3.180	3.144	3.120	3.096	3.242
CO • ICl	3.011	2.820	2.712	3.063	2.918
C_2H_2 • ICl	3.115	3.098	3.011	3.217	3.163
C_2H_4 • ICl	3.032	2.989	2.878	3.094	3.044
HCN • ICl	2.850	2.780	2.727	2.822	3.951
NH_3 • ICl	2.711	2.601	2.567	2.613	2.602
Sum of squares error		0.057	0.163	0.034	0.091
Variance (r^2)		0.70	0.42	0.77	0.65

6.4 Amine-ICl Complexes

Ab initio calculations were carried out at the B3LYP/6-31+G** level of theory using the improved basis set for iodine (referred to as SDD(p,d)) to investigate species that could be involved in the formation of the chiral amine-ICl complexes. The backbone

of the molecule, the 1,2,3,4,Tetrahydronaphthyl moiety, is relatively rigid and has only two conformational energy minima, where the amine is either in a *pseudo*-axial **166** or a *pseudo*-equatorial position **167**. The conformations are analogous to those observed in cyclohexenes and, for the sake of clarity, the phenyl moiety is not included in the figure below.

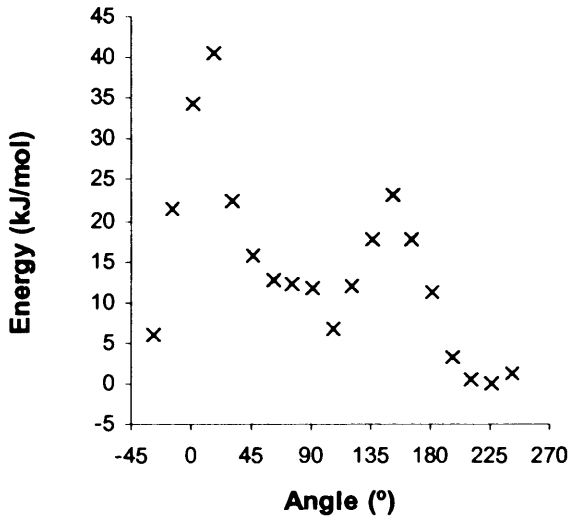


166 **167**

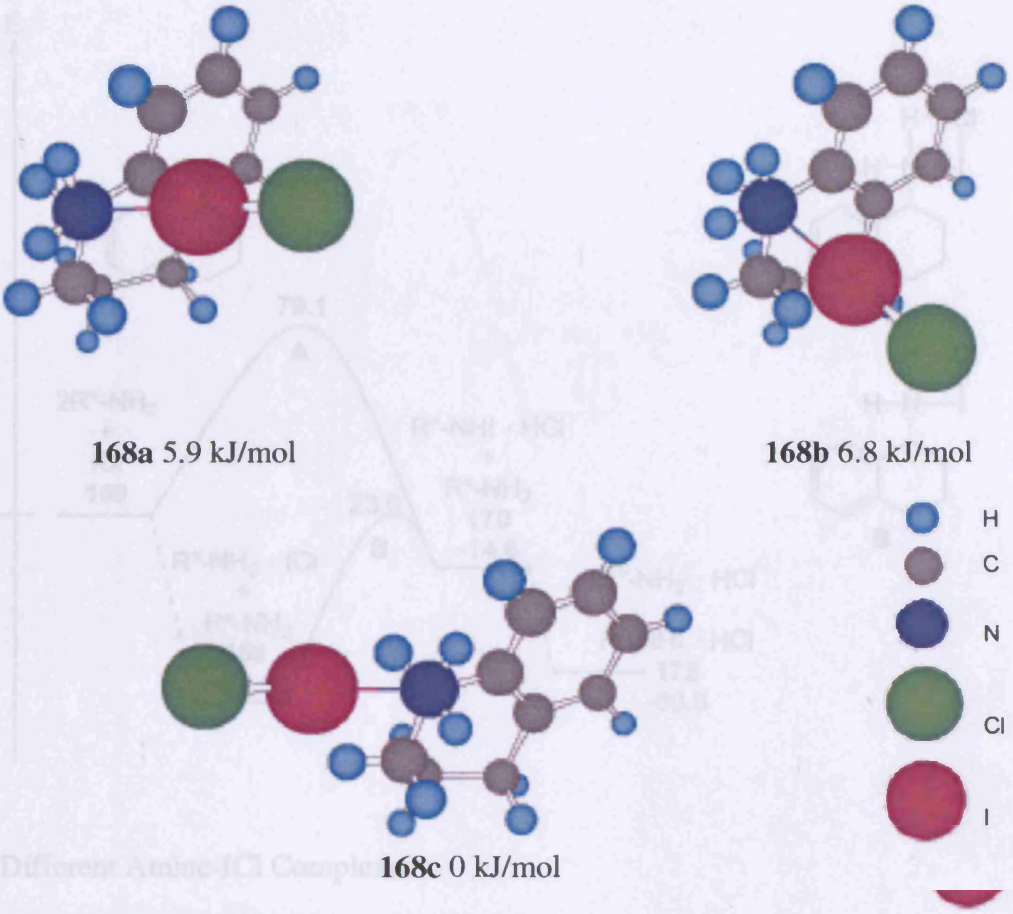
Fig. 6.1 The Two Possible Conformations of the Cyclohexene Moiety

Calculations show that the *pseudo*-axial conformation is lower in energy by 12 kJ/mol. It is therefore possible to conduct a conformational search by simply rotating around the N-C bond. The graph below shows a plot of energy against the C, C, N, I dihedral in 15° steps for amine-ICl complex **168a** starting from a local minimum obtained from a preliminary optimization.

Graph 6.2 Plot of Energy Against Rotation Around the C1, C2, N, I Dihedral



The two maxima arise from the eclipsed conformations, where the N-I bond interacts with bonds and substituents on the backbone. The second local minimum **168b** is due to the conformation where the iodine is located directly over the cyclohexene ring, and the third minimum **168c**, the global minimum is the reached when the Iodine is located approximately antiperiplanar to the aromatic moiety. These conformations are shown in a perspective looking down the C-N bond in the figure below.



168a 5.9 kJ/mol

168b 6.8 kJ/mol

168c 0 kJ/mol

Fig. 6.2 Local Minima obtained by Rotation Around the C-N Bond (energies given relative to the global minimum)

In this case it was considered unnecessary to continue the rotation through a full 360°, as this would bring the iodine back to its starting position via a third maximum. However, for structures where more than one halide is coordinating to the nitrogen, a full 360° rotation was carried out. The minima structures obtained for each of these rotations were then further minimised without constraints.

The formation of **168** is a straightforward donor-acceptor reaction between amine **169** and ICl. Species **170** involves a proton-iodine exchange on the nitrogen, while the formation of **171** could be facilitated by the formation of an HCl complex with another molecule of amine. This explains the need for a second equivalence of amine and is supported by the calculated energy of the amine HCl complex **172**.

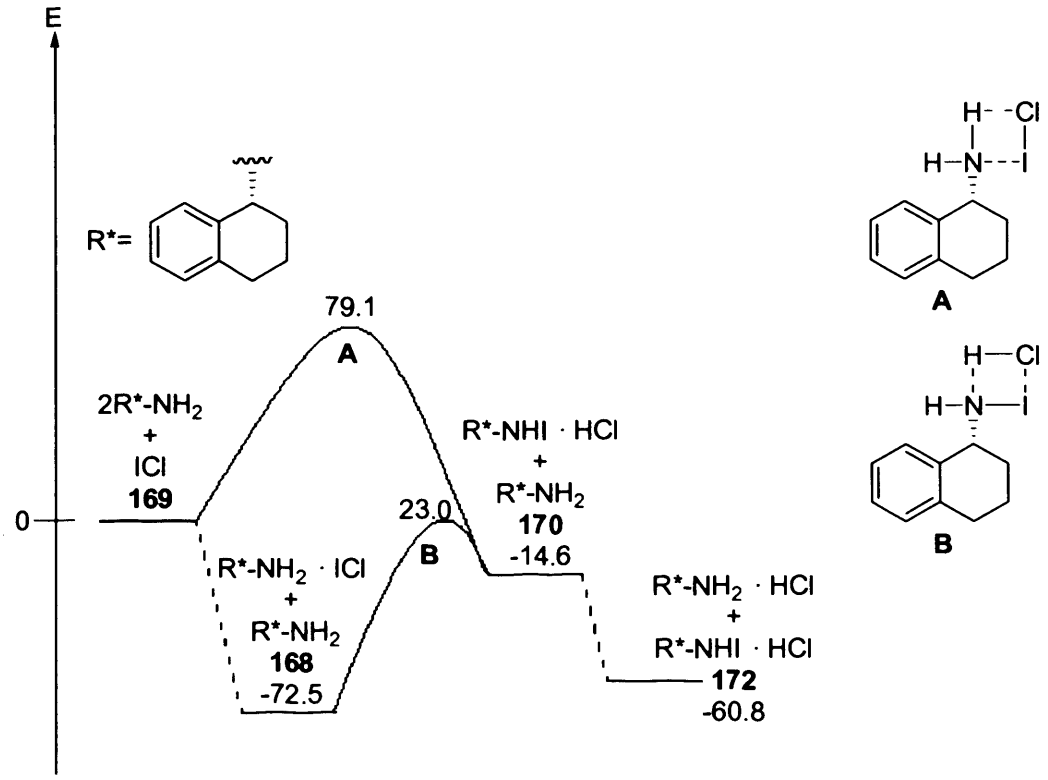


Fig 6.3 Different Amine-ICl Complexes

The second molecule of ICl necessary to form **171** (see fig. 6.4) or **173** must originate from **168**, as all of the ICl is assumed to be used initially in the formation of **168**, making the reactions leading to **171** and **173** side reactions. The formation of **171** can only take place if it is either assisted by the formation of an amine-HCl complex or if the complexation energy of **171** is much higher than that of **168**. Transition states **A** – **D** connecting the different complexes have also been considered. The energies of free molecules were recalculated in the basis set of the complexes in order to avoid basis set superposition errors (BSSE).

All energies shown in Fig 6.3 are relative to the free amine and have been corrected to ensure that they are all relative to the same number of atoms. Rotational analysis around the carbon–nitrogen bond for complexes **168** and **170-173** have been performed. Because the nitrogen atom in **170** is chiral, both diastereomers have been investigated. The energies shown in fig. 6.3 and 6.4 represent the energetic minima of all conformations calculated. The barrier **C** was too high to overcome at room temperature and **D** could not be located at all. As the initial complexation of the amine and ICl is so favorable, it is most likely that is formed via transition state **B**.

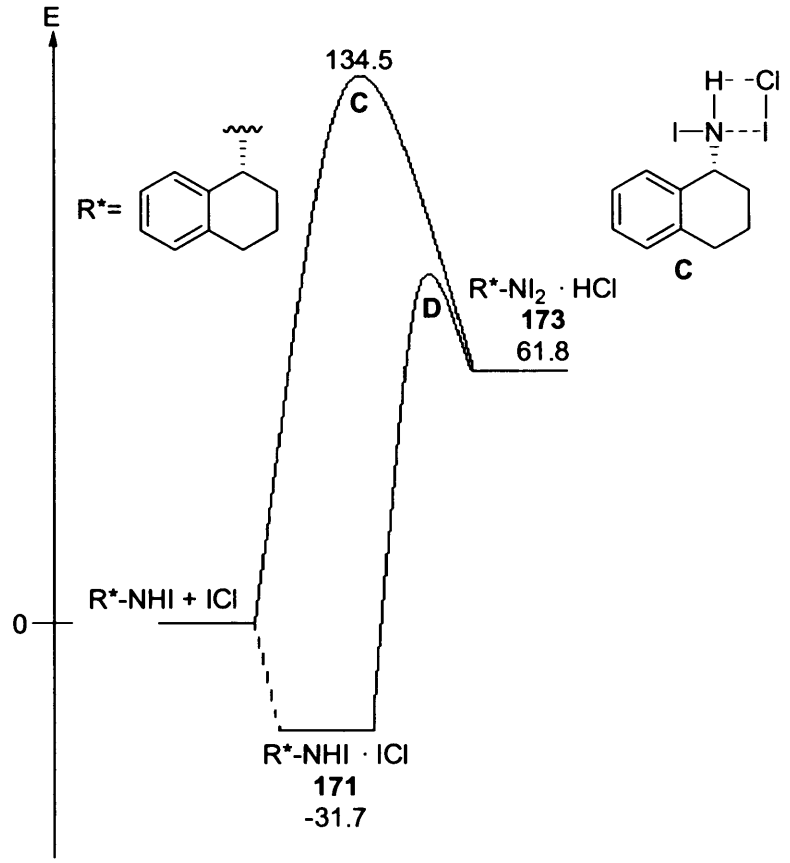


Fig 6.4 Different Amine-ICl Complexes

Since the stereoselectivity of the iodolactonization can be influenced drastically by changing the solvent used in the reaction, the Conductor Polarisable Continuum Model (PCM) was applied to the calculations of complexes **168** and **170**. The results obtained using the PCM model allow similar conclusions to those obtained by the previous calculations. The energies of the complexes are lower in the solvents in which stereoselectivities are higher, indicating a stabilization by the solvent. Solvents with a higher dielectric constant ε seem to stabilize the complexes more efficiently as shown in Table 6.3. The solvent plays an important role in the formation of the complexes and also in the subsequent addition to the alkene. The strong influence of the solvent on both reactivity and selectivity was already recognized in our preliminary experiments.

Table 6.3 Energies Obtained using the PCM Solvent Model.

solvent	benzene	diethyl ether	dichloromethane
ε (pF/m)	2.25	4.36	8.93
168	-87.8	-103.3	-106.0
170	-23.3	-33.9	-36.5

Energies given in kJ/mol relative to free amine and ICl also calculated in solution.

Selectivity in the iodolactonization of **118** is thought to procede via the formation of complex **168** when the reaction mixture of ICl and amine **169** are cooled down to –78 °C and the reaction is commenced immediately. When the mixture of ICl and **169** was stirred at room temperature for 30 minutes before the addition of **118** at –78°C, which was found to give higher selectivities, **170** or a mixture together with **168** may be the dominant source of selectivity. This hypothesis is supported by the isolation of α-tetralone after longer reaction times (>30 minutes) between ICl and **169**, which might originate from **170** after an HI elimination to the imine and subsequent aqueous workup.

A series of calculations was also carried out to take a closer look at this side reaction. Assuming that **170** is present and that the HCl released during its formation has formed a complex with a free amine molecule, a transition state for the formation of imine **174** from iodinate amine **175** was sought. The energies, relative to **175** are shown in the figure below.

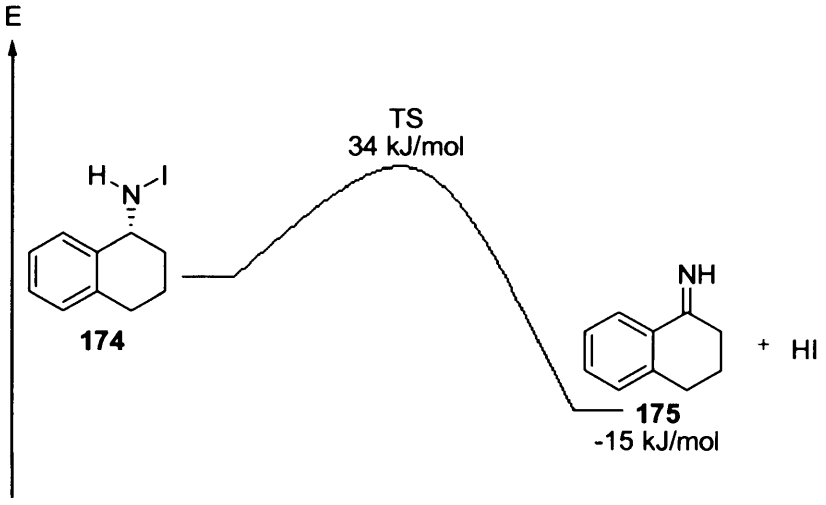


Fig 6.5 Investigation of Imine Formation

The Barrier is low enough to be overcome at room temperature. The transition state in this reaction can only be seen as an approximation, as it is likely that Cl^- assists in the process. These calculations provide further evidence for the presence of **175** and/or **170**.

Screening of amines for these reaction has shown that nonbenzylic amines generally perform worse than benzylic amines. Similarly, selectivity is generally lower when the substrate does not contain an aromatic moiety. This suggests the possibility of a π-stacking interaction between chiral amine complex and the substrate. To model such interactions, it is normally necessary perform calculations using Møller-Plesset perturbation theory with large basis sets, which is extremely computationally demanding. Recent work by J. Platts and coworkers[108] has shown that it is possible to obtain comparable results, using BH&H hybrid density functional methods, at a fraction of the computational times. Attempts were made to model π-stacking interactions between the complex and the substrate with a view to modeling a transition state for the lactonisation reaction. Preliminary results were promising, but as soon as iodine was incorporated into the system convergence failures were experienced.

6.5 Continuous Chirality measurement (CCM)

Continuous Chirality Measurement (CCM) is a method developed by Avnir and co-workers to quantify chirality.[109] This is achieved by considering molecules as a series of points in space joined together to form an object. This object is then distorted to give the nearest symmetrical (non-chiral) conformation of the molecule. The CCM measure of chirality is then given by the root mean square of the distance between any given point and its equivalent point in the non-chiral conformation:

$$S = \frac{100}{nD^2}\sum_{i=1}^{n}(p_i - \hat{p}_i)^2$$

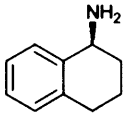
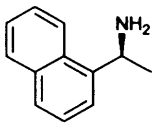
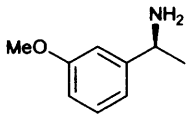
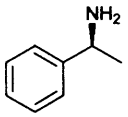
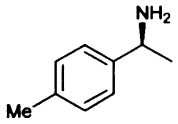
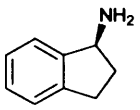
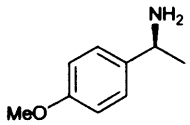
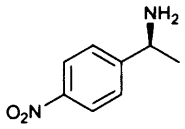
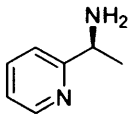
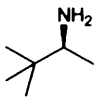
Equ 6.4 Calculation of the CCM Term

Where n is the number of points in space, p_i and $\hat{p}_i$ are pairs of points in the chiral and non-chiral conformations and D is a scaling factor to ensure that the overall size of the molecule is irrelevant.

Although this method was originally developed to investigate the relationship between the chirality of various inhibitors or agonists and the binding energies to their respective receptors in biological systems,[110] more recent work by Lipkowitz et al.[111] has shown that the results of CCM calculations can be used to predict enantiomeric excesses (*ee*) in asymmetric reactions. This is achieved by calculating the CCM values of a series of chiral catalysts or ligands which are known to produce different *ee*. If a correlation can be found between *ee* and the chirality measurement, it is possible to predict whether or not a new catalyst or ligand will be active.

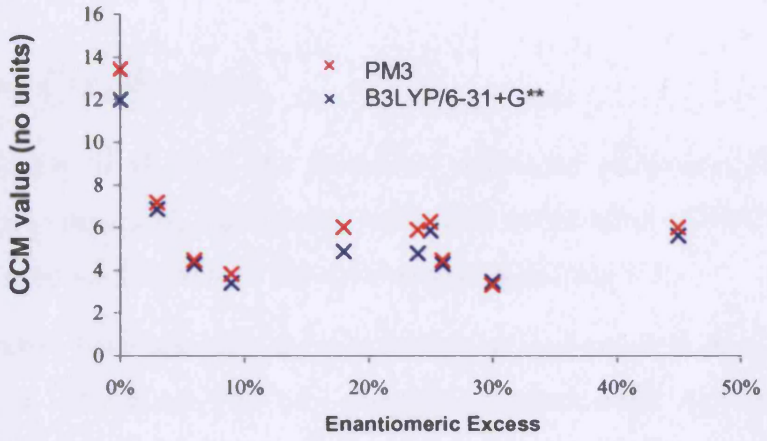
A set of 10 ligands which have already been screened for activity in stereocontrolled iodolactonisation were pre-optimised using the PM3 semi-empirical method and subsequently further optimised at the B3LYP/6-31G** level of theory. CCM calculations were carried on both the MP3 and DFT optimized structures. The results are shown in the table below:

Table 6.4 CCM Values for a set of ICl Ligands which Produce a Known *ee* in Iodolactone **46**

Ligand	CCM (PMP)	CCM (B3LYP/631G**)	*ee* (%)
	5.6037	5.9838	45%
	3.4490	3.2897	30%
	4.2673	4.4498	26%
	5.8520	6.2441	25%
	4.7642	5.8768	24%
	4.8546	5.9942	18%
	3.3773	3.8105	9%
	4.2776	4.4421	6%
	6.8434	7.1547	3%
	11.9615	13.3872	0%

It is immediately apparent there is no linear relationship between the CCM values above and the corresponding *ee* (see graph 6.3). There is also no polynomial relationship, similar to the one observed by Lipkowitz, may be present:[112]

Graph 6.3 Plot of CCM Values Against *ee*



6.6 Conclusions

Computational results suggest that after initial complexation of the chiral amine with ICl, an exchange of iodine for a proton on the amine takes place. The HCl produced then forms a complex with a second amine molecule, thus explaining the need for two equivalents of amine in this reaction. Calculations also show that subsequent elimination of HI to form an imine is energetically favourable. This side reaction explains the presence of the corresponding ketone after work up and the decrease in enantioselectivity observed when the optimum complexation time of 30 min. before addition of the substrate is exceeded. These results would suggest, that in order to obtain higher selectivities, it will be necessary to synthesise amine on tertiary carbon centres. The elimination reaction described above would not be possible if such a ligand were employed.

The disappointing results obtained are probably be due to the structure of the ligands investigated. Most of the chiral amine ligands in this set of calculations are relatively planar, with only a few atoms above and below the plane, leading to very low CCM values. This method was optimised for larger and more complex molecules and it may be necessary to alter the algorithm to make it more suitable for this system. The problem is exemplified by the large difference in the CCM values for the eighth and

ninth ligand shown in the table. As the structures are very similar, one would have expected very similar CCM values.

Chapter 7

Outlook and Conclusions

It has been possible to improve the previously optimised reaction conditions and obtain reproducible results by maintaining a constant temperature of 33°C during the 30 min. complexation time between the chiral amine ligand and ICl.

A number of amines have been synthesised or acquired and tested as chiral ligands in the stereoselective iodolactonisation of 4-phenyl-4-pentenoic acid. Although, in most cases, enantiomeric excess has been observed in the product, none have performed better than the commercially available 1,2,3,4-tetrahydronaphthyl-1-amine. The bidentate amine ligands **149** and **150** provided an interesting result. Amine **149** displayed low selectivity and no reaction at all was observed when amine **150** was employed. As theses amine are so similar in structure it may be possible to tune the electronics of the system by including different substituents and thereby optimising the reaction. Alternative ligands have also been tested and it has been shown that phosphorous based ligands are not suitable for this reaction. Chiral diselenides can be used as ligands in conjunction with *N*-halosuccinamides but do not lead to significant stereoselectivities. No reaction was observed when silver salts were employed as alternative electrophiles.

It had been hoped that, by increasing the steric hindrance on the double bond of the substrate, it would be possible to slow the reaction, thereby increasing selectivity, but it has been shown that this is not the case. Interestingly, it has been demonstrated that similar selectivities can be obtained in substrates that contain *trans*-disubstituted double bonds, a group of molecules previously untested.

Computational results suggest that after initial complexation of the chiral amine with ICl, an exchange of iodine for a proton on the amine takes place. The HCl produced then forms a complex with a second amine molecule, thus explaining the need for two equivalents of amine in this reaction. Calculations also show that subsequent elimination of HI to form an imine is energetically favourable. This side reaction explains the presence of the corresponding ketone after work up and the decrease in

enantioselectivity observed when the optimum complexation time of 30 min. before addition of the substrate is exceeded. These results would suggest that, in order to obtain higher selectivities, it will be necessary to synthesise amine on tertiary carbon centres. The most promising results in the synthesis of this type of amine were obtained through the addition of Leighton's chiral allylsilane to benzoylhydrazones and more work should be carried out to improve on this reaction and the subsequent cleavage to the free amine. Another class of compounds, which has not yet been tested, are chiral sulphonamides. These may prove to be useful chiral ligands, as coordination to the sulphur would bring the iodine even closer to the chiral centre.

Chapter 8

Experimental

General Comments

All experiments were carried out using standard laboratory equipment. Reactions requiring the exclusion of oxygen and water were carried out under an argon atmosphere in oven-dried glassware. Precise, constant working temperatures were obtained using hot-plates fitted with temperature probes in oil baths. Cooling baths at –78°C were prepared from dry ice and acetone. When constant cooling over long periods was required a *Haake EK 90* immersion cryostat was employed.

THF and diethyl ether were all freshly distilled over sodium/benzophenone under N_2. CH_2Cl_2 was distilled over calcium hydride and diisopropylamine over potassium hydroxide. Any other anhydrous solvents used were purchased in sealed containers fitted with septa.

Physical Data

^{1}H-NMR-Spectroscopy

Bruker DPX 400 (400 MHz), Bruker Ultrashield 500/54mm (500 MHz)

Chemical shifts δ are given in ppm relative to an internal standard (usually TMS in deuterated chloroform). Coupling constants J are given in Hertz. The multiplicity of signals is denoted as follows; s = singlet, d = doublet, t = triplet, q = quartet, qin = quintet, m = unresolved multiplet.

^{13}C-NMR- Spectroscopy

Bruker DPX 400 (100 MHz), Bruker Ultrashield 500/54mm (125 MHz)

Chemical shifts δ are given in ppm relative to an internal standard (usually TMS in deuterated chloroform).

^{31}P-NMR- Spectroscopy

Jeol Eclipse 300 (300 MHz)

Chemical shifts δ are given in ppm relative to 85% Phosphoric acid

Mass Spectrometry

Fision VG Platorm

Analyses performed in the mass spectrometry laboratory of Cardiff University chemistry department. Ionisation was atmospheric pressure chemical ionisation (APCI).

Accurate high resolution mass spectroscopic data was obtained from the EPSRC mass spectrometry service centre at Swansea University. Molecular formulae are quoted in either molecular ions (M^+), molecular ion + proton ($M+H^+$) or molecular ion + ammonium ($M+NH_4^+$). All values are given in atomic mass units per elementary charge (m/z). The intensity relative to the base peak (strongest signal) is given in brackets.

Gas Chromatography/Mass Spectrometry

Varian Saturn 3400 GC/MS

Experiments carried out using a standard, 30m, DB 5-MS column with an inner diameter of 0.5 mm. The injector temperature was set to 250°C and the carrier gas was helium set to 12 psi. Ion were generated by Electronic Ionisation and analysed by a *Varian Ultratrace* ion trap. Column conditions were varied between experiments.

IR-Spectroscopy

Perkin Elmer 1600 FTIR spectrometer

Wave number quoted in cm^{-1}. All samples were either measured as liquid films on chloride plates or press into KBr pellets.

Optical rotation

Measurements carried out on an *Optical Activity Ltd. AA-1000* polarimeter at a wavelength of 589 nm, cell length 5 cm, concentration C given in g/100ml.

Melting points

Electrothermal melting apparatus

Melting points of all compounds were measured in an open capillary tube and are uncorrected.

Chromatography

Thin layer chromatography was performed on Merck silica gel 60 F 254 precoated aluminium backed plates. Plates were visualised, either by ultraviolet-fluorescence or by development with either basic, aqueous potassium permanganate, 5 wt % phosphomolybdic acid in ethanol or acidic vanillin in ethanol. Preparative work was carried out using glass backed MN silica gel 60 F 254 plates.

Flash Chromatography

Flash chromatography was carried out using Fisher silica gel 60 (35-70 mesh), eluents are given for each product as a solvent ratio.

High performance liquid chromatography

a) *Merck-Hitachi L6200* gradient pump in conjunction with *Merck-Hitachi L4200 UV/Vis* detector and *Merck-Hitachi L2500.*

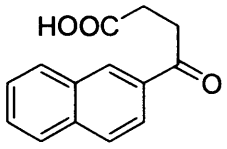
b) *Shimadzu LC-10AT-VP* solvent delivery system, *Shimadzu SPD-M10a-VP DAD* diode array detector operating on *Shimadzu Class VP software.*

Analytical columns used for separation were the Chiralcel (OB, OB-H, OD, OD-H, AD, OD-OJ) from Diacel industries and Regis Whelk-O1 column length 25 cm, diameter 0.46mm, solvent flow rates were set at 0.5 ml/min for analytical work. Preparative work was carried out on a Chiralcel OD preparative column, column length 25 cm, diameter 2cm, flow varied according to experiment. The average experimental error for the determination of *ee* using this method is ± 0.5%.

General procedure for iodocyclizations:

The enantiomerically pure amine (0.46 mmol) was dissolved in CH_2Cl_2 (3 mL) and stirred with ICl (0.23 mmol, 0.23 mL of a 1M solution in CH_2Cl_2 for 30 min at 33 °C. After cooling to -78°C, the unsaturated carboxylic acid (0.115 mmol) dissolved in CH_2Cl_2 (1 mL), was added. After 10 min, aqueous $Na_2S_2O_3$ (10%) was added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was extracted with CH_2Cl_2 (2x 6 mL) and the combined organic layers were dried with $MgSO_4$. The product was purified by preparative TLC (*tert*-butylmethyl ether/pentane 1:2).

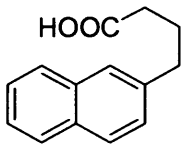
4-(Naphthalen-2-yl)-4-oxobutanoic acid 61a:[31]



Prepared via the Friedel-Crafts acylation of naphthalene (2g, 15.6 mmol) with succinic anhydride, a 17:3 ratio of regioisomers (as estimated by NMR) was obtained in 56% yield according to the procedure of Huggenberg and Hesse.[31] The isomers were not separated at this stage and for the sake of clarity only the spectrum of the major isomer is shown below. For further spectroscopic data see reference.[31]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.80 (t, J = 7.2, 2H, CH_2-C=O), 3.43 (t, J = 7.2, 2H, CH_2-COOH), 7.73-7.48 (m, 2H, Ar), 7.75-8.23 (m, 4H, Ar) 8.51 (s, 1H, Ar) ppm.

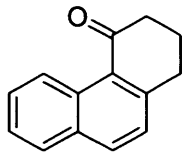
4-(Naphthalen-2-yl)butanoic acid 62a:[31]



A mixture of ketones **61a** and **61b** (200 mg, 0.88 mmol), diethylene glycol (20 mL), hydrazine monohydrate (1 mL), and KOH (1g) was refluxed for 6 h, cooled to room temperature, and poured into excess water. The product was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were washed with water and dried over $MgSO_4$. The crude product, obtained after evaporation of the solvent was purified by recrystalisation from ethanol/water. 147 mg of a grey crystalline solid were obtained in 78%. The isomers were not separated at this stage and for the sake of clarity only the spectrum of the major isomer is shown below. For further spectroscopic data see reference.[31]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.13 (m, 2H, CH_2-*CH_2*-CH_2), 2.42 (t, J = 10, 2H, *CH_2*-COOH), 2.87 (t, J = 13, 2H, CH_2-Ar), 7.28-7.55 (m, 3H, Ar), 7.63 (s, 1H, Ar), 7.67-7.95 (m, 3H, Ar) ppm.

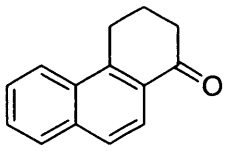
4-Oxo-1,2,3,4-tetrahydrophenanthren 58a:[31]



Prepared from a mixture **62a** and **62b** (100 mg, 0.46 mmol) by cyclisation with polyphosphoric acid according to the procedure of Huggenberg and Hesse.[31] The product was isolated in 76% yield as a colourless crystalline materiel, mp = 65-67°C. For further spectroscopic data see reference.[31]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.17-2.23 (m, 2H, CH_2-*CH_2*-CH_2), 2.79 (t, J = 6.2 Hz, 2H, *CH_2*-Ar), 3.13 (t, J = 6.2 Hz, 2H, *CH_2*-C=O), 7.33 (d, J = 8.4 Hz, 1H, Ar), 7.47-7.51 (m, 1H, Ar), 7.61-7.65 (m, 1H, Ar), 7.81 (dd, J = 7.91, 1.3 Hz, 1H, Ar), 7.93 (d, J = 8.4 Hz, 1H, Ar), 9.41 (d, J = 8.8,1H, Ar) ppm.

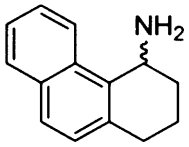
3,4-Dihydrophenanthren-1(2*H*)-one 58b:[31]



Isolated in 13% yield as a colourless crystalline materiel, mp = 93-94°C, as a by-product in the preparation of **58a**. For further spectroscopic data see reference.[31]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.16-2.22 (m, 2H, CH_2-*CH_2*-CH_2), 2.75 (t, J = 6.9 Hz, 2H, *CH_2*-Ar), 3.37 (t, J = 6.1 Hz, 2H, *CH_2*-C=O), 7.50-7.71 (m, 2H, Ar), 7.76 (d, J =10, 1H, Ar), 7.81-7.93 (m, 2H, Ar), 8.04-8.25 (m, 1H, Ar) ppm.

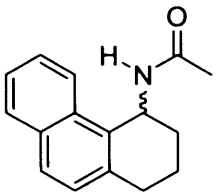
1,2,3,4-Tetrahydrophenanthren-4-amine 63:



Prepared in 53% yield by reductive amination of **58a** (100 mg,0.5 mmol) with sodium cyanoborohydride and ammonium acetate according to the procedure of Perkle *et al.*[29] As the product was not isolated in literature, full characterisation is given below.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.7-2.05 (m, 4H, $2CH_2$), 2.76-2.90 (m, 2H, C*H_2*-Ar), 4.64 (s, 1H, C*H*-NH_2), 7.10 (d, J = 8.4 Hz, 1H, Ar), 7.34 (dt, J = 7.1 Hz, 0.9 Hz, 1H, Ar), 7.44 (dt, J = 7.0 Hz, 1.3 Hz, 1H, Ar), 7.56 (d, J = 8.4 Hz, 1H, Ar), 7.71 (d, J = 8.1 Hz, 1H, Ar), 8.08 (d, J = 8.5 Hz, 1H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.1 (*C*H_2), 30.3 (*C*H_2-Ar), 31.9 (*C*H_2-$CHNH_2$), 44.5 (*C*H-NH_2), 123.3 (*C*H, Ar), 124.8 (*C*H, Ar), 126.4 (*C*H, Ar), 127.1 (*C*H, Ar), 128.2 (*C*H, Ar), 128.8 (*C*H, Ar), 132.0 (*C*, Ar), 132.7 (*C*, Ar), 133.9 (*C*, Ar), 134.8 (*C*, Ar) ppm; IR (thin film): ν = 2926, 2360, 1508, 1442, 1262, 806, 742, 668 cm^{-1}; MS *m/z* (%): 198 (13) [M^+], 181 (25), 180 (100), 168 (33), 154 (31), 84 (16), 69 (15), 57 (16), 43 (21), 40 (25); HRMS: calcd. for $[C_{14}H_{15}N+H]^+$: 198.1277, found: 198.1280.

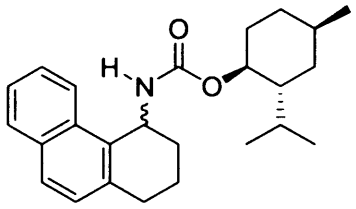
1,2,3,4-Tetrahydrophenanthren-4-yl acetamide 64:



Recovered in 37% yield as a by-product from the synthesis of **63** as a colourless crystalline material. No melting point was measured, as the product decomposed above 180 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 1.51 (s, 3H, CH_3), 1.73-1.95 (m, 3H, CH_2), 2.16-2.27 (m, 1H, CH_2), 2.83-2.91 (m, 2H, Ar-CH_2-CH_2), 5.67 (s, 1H, C*H*NHR), 7.12 (d, J = 8.0 Hz, 1H, Ar), 7.43 (dt, J =5.4 Hz, 1.3 Hz, 2H, Ar), 7.64 (d, J = 8.4 Hz, 1H, Ar), 7.72 (d, J = 7.8 Hz, 1H, Ar), 7.87 (d, J = 8.5 Hz, 1H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.9 (*C*H_2), 22.1 (*C*H_3), 28.3 (*C*H2-Ar), 28.8 (*C*H_2-CHNHR), 42.3 (*C*H-NH_2), 121.5 (*C*H, Ar), 123.9 (*C*H, Ar), 125.4 (*C*H, Ar), 126.5 (*C*H, Ar), 126.9 (*C*H, Ar), 127.2 (*C*H, Ar), 129.0 (*C*, Ar), 131.7 (*C*, Ar), 131.9 (*C*, Ar), 134.2 (*C*, Ar), 167.3 (*C*=O) ppm; IR (KBr): ν = 7629, 1598, 1335, 1098, 1026, 934, 823, 731 cm^{-1}; MS *m/z* (%): 240 (8) [M$^+$], 180 (100), 175 (55), 152 (27), 139 (15), 89 (16), 76 (15), 63 (16), 51 (21); HRMS: calcd. for [$C_{16}H_{17}N$+H]$^+$: 240.1383; found: 240.1384.

(1*R*,2*S*,5*R*)-*N*-Menthoxycarbonyl-4-(1,2,3,4-tetrahydrophenanthryl) amine 65:[33]

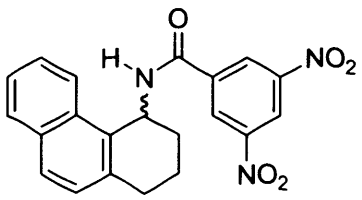


Synthesised in 42 % yield from **63** (65 mg, 0.33 mmol) by treatment with (1*R*, 2*S*, 5*R*)-(-)-menthyl chloroformate according to the procedure of Perkle *et al.*[33] No melting point was measured, as the product decomposed above 150 °C. For the sake

of clarity the spectrum of only one diastereoisomer (the title compound) is shown below. For further spectroscopic data see reference.[33]

^{1}H-NMR ($CDCl_3$ 400 MHz): δ = 0.7 (d, J = 7, 3H, CH_3), 0.78 (d, J = 7, 3H, CH_3), 0.83 (d, J = 7, 3H, CH_3), 0.9-1.23 (m, 2H, CH_2), 1.40-1.52 (m, 2H, CH_2), 1.52-1.65 (m, 2H, CH_2), 1.65-1.92 (m, 4H, CH_2), 1.97-2.04 (m, 1H, CH), 1.15-1.29 (m,1H, CH), 2.77-2.92 (m, 2H, CH_2-Ar), 4.70 (td, J=10.8, 4.3, 1H, CH-OR), 4.86 (t, J = 7.9, 1H, CH-NHR), 5.41 (d, J = 7.9, 1H, NHR), 7.20 (d, J=8.5, 1H, Ar), 7.32-7.42 (m, 2H, Ar), 7.61(d, J = 8.4, 1H, Ar), 7.81 (d, J = 7.6, 1H, Ar), 7.9 (d, J = 8.2, 1H, Ar) ppm.

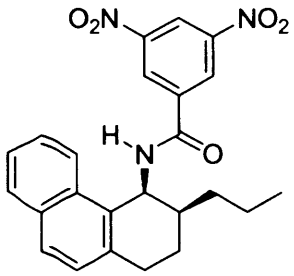
4-(3,5-Dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene 67:[29]



Synthesised in 97% yield from **63** (130 mg, 0.66 mmol) according to the procedure of Perkle *et al.*[29] No melting point was measured, as the product decomposed above 135 °C. For further spectroscopic data see reference.[29]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.93 (m, 1H, CH_2-CHNHR), 2.03 (m, 2H, CH_2-CH_2-CH_2), 2.43 (m, 1H, CH_2-CHNHR), 3.03 (m, 2H, CH_2-Ar), 5.99 (m, 1H, CH-NHR), 6.56 (d, J=7.3 Hz, 1H, Ar), 7.27 (d, J=8.5 Hz, 1H, Ar), 7.43 (ddd, J=1.5, 6.8, 7.8 Hz, 1H, Ar), 7.48 (ddd, J=1.7, 6.8, 8.3 Hz, 1H, Ar), 7.76 (d, J=8.5 Hz, 1H, Ar), 7.81 (dd, J=1.5, 7.8 Hz, 1H, Ar), 7.87 (d, J=8.3 Hz, 1H, Ar), 8.86 (d, J=1.8 Hz, 2H, Ar), 9.10 (t, J=1.8 Hz, 1H, Ar) ppm.

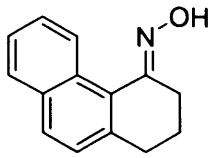
(3*R*,4*R*)-4-(3,5-Dinitrobenzamido)-3-propyl-1,2,3,4-tetrahydrophenanathrene 69:



(3*R*,4*R*)-*trans*-4-(3,5-Dinitrobenzamido)-3-propenyl-1,2,3,4-tetrahydrophenanthrene **68** (500 mg, 1.15 mmol) was dissolved in a 1:1 mixture of dry THF/2-propanol (5 mL). Wilkinsons catalyst (0.5 mol%) was added and the mixture was stirred under hydrogen for 48 h. The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel, petroleum ether/Et_2O 4:1). 464 mg of a pale yellow powdery solid (93% yield) were obtained. No melting point was measured, as the product decomposed above 130°C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.89 (t, *J*=7.6 Hz, 3 H, C*H*$_3$), 1.14–1.31 (m, 1H, C*H*-CHCNHR), 1.41–1.72 (m, 4H, CH-C*H*$_2$-C*H*$_2$-CH_3), 1.92–2.04 (m, 2 H, CH_2-C*H*$_2$-CH), 2.94–3.10 (m, 2H, C*H*$_2$-Ar), 5.98 (dd, *J*=9.5, 3.4 Hz, 1H, C*H*-NHR), 6.26 (d, *J*=9.5 Hz, 1H, Ar), 7.10 (d, J=8.5 Hz, 1H, Ar) 7.33 (t, *J*=7.3 Hz, 1H, Ar), 7.43 (dt, *J*=7.8, 1.1 Hz, 1H, Ar), 7.42 (d, *J*= 8.5 Hz, 1H, Ar), 7.52 (d, *J*=8.5 Hz, 1 H, Ar), 8.00 (d, *J*=8.5 Hz, 1H, Ar), 8.73 (d, *J*= 2.0 Hz, 2H, Ar), 8.95 (t, *J*=2.1 Hz, 1H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 14.8 (*C*H_3), 20.9 (*C*H_2-CH_3), 24.0, 30.8 (*C*H_2-Ar), 34.9 (*CH*$_2$-*C*H), 39.8 (*C*H), 48.1 (*C*H-NHR), 121.4 (*C*H, Ar), 122.0 (*C*H, Ar), 125.9 (*C*H, Ar), 127.5 (*C*H, Ar), 127.7 (*C*H, Ar), 128.1 (2*C*H, Ar), 129.1 (*C*H, Ar), 130.9 (*C*, Ar), 132.3 (*C*, Ar), 132.8 (*C*, Ar), 135.8 (*C*, Ar), 138.2 (*C*, Ar), 148.8 (2*C*-NO_2), 162.2 (*C*=O) ppm; IR (KBr): ν = 3339, 7632, 1541, 1526, 1345, 1083, 913, 804, 729 cm^{-1}; MS: m/z (%): 433.3 (37) [M]+, 432.3 (100), 210.1 (20), 166.8 (24), 62.0 (8); HRMS: calcd for $C_{24}H_{24}N_3O_5$ [M+H]$^+$: 434.1710; found: 434.1715.

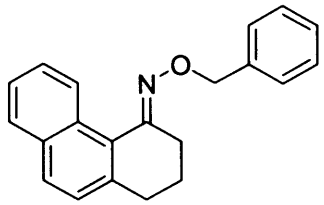
1,2,3,4,-Tetrahydrophenanthren-4-one oxime 70:



4-Oxo-1,2,3,4-tetrahydrophenanthren **58a** (196 mg, 1.0 mmol) was dissolved in 10ml of a 1:1 mixture of H_2O and ethanol. Hydroxylamine hydrochloride (136 mg, 2.0 mmol) and sodium acetate (205 mg, 2.5 mmol) were added and the mixture was allowed to stir overnight. The resulting precipitate was filtered and washed with H_2O, redissolved in diethyl ether and again washed with H_2O. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to yield 180 mg (85% yield) of a colourless crystalline product, mp = 162-164°C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.74-1.84 (m, 2H, CH_2-C*H*$_2$-CH_2), 2.76 (t, J = 5.1 Hz, 2H, C*H*$_2$-Ar), 2.88 (t, J = 6.9 Hz, 2H, C*H*$_2$-C=NOH), 7.19 (t, J = 8.3 Hz, 1H, Ar), 7.34 (dt, J = 1.1, 5.8 Hz, 1H, Ar), 7.45 (dt, J = 1.4, 5.4 Hz, 1H, Ar), 7.68 (d, J = 8.3 Hz, 1H, Ar), 7.74 (d, J = 8.1 Hz, 1H, Ar), 8.83 (d, J = 8.7 Hz, 1H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.1 (*C*H$_2$-CNOH), 25.3 (CH_2-*C*H$_2$-CH_2), 31.4 (*C*H$_2$-Ar), 125.2 (*C*H, Ar), 126.6 (*C*H, Ar), 136.7 (*C*H, Ar), 126.8 (*C*H, Ar), 127.0 (*C*H, Ar), 128.4 (*C*H, Ar), 129.5 (*C*, Ar), 130.5 (*C*, Ar), 133.3 (*C*, Ar), 140.6 (*C*, Ar), 156.7 (*C*=NOH) ppm; IR (KBr): ν = 3050, 1620, 1450, 1350, 1140, 980, 930, 750 cm^{-1}; MS (EI) *m/z* (%): 212 (14) [M$^+$], 211 (80), 194 (100), 183 (75), 166 (78), 152 (52), 140 (85), 115 (41), 63 (38); HRMS: calcd. for $[C_{14}H_{13}O+H]^+$ 212.1075, found 212.1069.

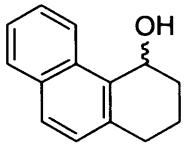
(*E*)-2,3-Dihydrophenanthren-4(1*H*)-one 4-benzyl oxime 71:



A solution of 1,2,3,4,-tetrahydrophenanthren-4-one oxime **70** (150 mg, 0.71 mmol) in DMF (10 ml) was added to a suspension of sodium hydride (31 mg, 0.89 mmol) in DMF (1 ml) cooled to 0°C. The reaction mixture was allowed to stir for 30 min. at 0°C. Benzyl chloride (151 mg, 0.89 mmol) was then added and the solution was allowed to stir for 16 hours, warming to room temperature. Water (5ml) was then added and the mixture was extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed twice with water, then with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product purified by flash chromatography (silica gel, petroleum ether/Et_2O 3:1). The product was obtained in 83% in the form of a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.68-1.85 (m, 2H), 2.21-2.57 (m, 2H), 2.86-2.91 (m, 2H), 4.80 (m, 2H,), 7.16 (d, lH, J = 8.5 Hz, Ar), 7.29-7.48 (m, 7H, Ar), 7.64 (d, lH, J = 8.5 Hz, Ar), 7.73 (dd, lH, J = 8.4, 1.4 Hz, Ar), 8.00 (d, 1H, J = 8.0 Hz, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.1 (*C*H_2-CNOBn), 25.3 (CH_2-*C*H_2-CH_2), 31.4 (*C*H_2-Ar), 76.9 (*C*H_2-Ph), 122.5 (*C*H, Ar), 124.8 (*C*H, Ar), 126.6 (*C*H, Ar), 127.9 (*C*H, Ar), 128.0 (*C*H, Ar), 128.0 (*C*H, Ar), 128.4 (*C*H, Ar), 128.6 (*C*H, Ar), 128.7 (*C*H, Ar), 132.4 (*C*H, Ar), 136.9 (*C*H, Ar), 138.2 (*C*H, Ar), 130.5 (*C*, Ar), 133.3 (*C*, Ar), 140.6 (*C*, Ar), 156.7 (*C*=NOBn) ppm; IR (thin film): ν = 3052, 1619, 1463, 1350, 1140, 983, 929, 835, 752 cm^{-1} MS (EI) *m/z* (%): 301 (12) [M^+], 194 (100), 183 (73), 166 (68), 152 (42), 140 (75), 115 (43), 63 (39); HRMS: calcd. for $[C_{21}H_{19}NO+H]^+$ 302.3896, found 302.3894.

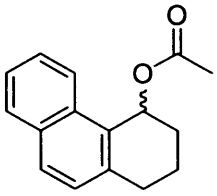
1,2,3,4-Tetrahydrophenanthren-4-ol 73:



$NaBH_4$ (62 mg, 1.68 mmol) was added to a solution of 2,3-dihydrophenanthren-4-(1*H*)-one **58a** (300 mg, 1.53 mmol) in MeOH at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h. The solvent was evaporated and the residue treated with sat. aq. NH_4Cl (3 mL) and extracted with CH_2Cl_2 (4 x 3 mL). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated to yield 298 mg (98% yield) of a colourless crystalline product mp = 171-173°C.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.68-2.04 (m, 3H, Ar-CH_2-C*H*H-CH_2), 2.11-2.20 (m, 1H, CH_2-C*H*H-CH_2), 2.71-2.89 (m, 2H, CH_2-Ar), 5.31 (t, J = 3.3 Hz, 1H, C*H*-OH), 7.14 (d, J = 8.5 Hz, 1H, Ar), 7.34 (dt, J = 7.4 Hz, J = 0.7 Hz, 1H, Ar), 7.46 (dt, J = 7.0 Hz, J = 1.4 Hz, 1H, Ar), 7.59 (d, J = 8.4Hz, 1H, Ar), 7.68 (d, J = 8.1 Hz, 1H, Ar), 8.13 (d, J = 8.5 Hz, 1H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.2 (CH_2-*C*H_2-CH_2), 30.3 (*C*H_2-Ar), 31.7 (*C*H_2-CHOH), 63.5 (*C*H-OH), 123.4 (*C*H, Ar), 125.1 (*C*H, Ar), 126.6 (*C*H, Ar), 128.0 (*C*H, Ar), 128.2 (*C*H, Ar), 128.6 (*C*H, Ar), 132.0 (*C*, Ar), 132.4 (*C*, Ar), 132.6 (*C*, Ar), 135.3 (*C*, Ar) ppm; IR (KBr): ν = 3428, 2990, 2940, 2872 cm^{-1}; MS (EI) *m/z* (%): 198 (83) [M^+], 180 (100), 164 (62), 152 (27), 140 (77), 115 (38) 90 (26), 76 (21), 63 (25); HRMS: calcd. for $C_{14}H_{14}O$+NH_4^+ 216.1383, found 216.1385.

1,2,3,4-Tetrahydro-phenanthrenyl-4-acetate 74:



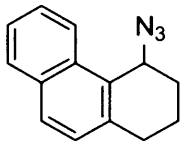
DMAP (60 mg, 0.51 mmol) and acetyl chloride (40 mg, 0.51 mmol) were added to a solution of **73** (100 mg, 0.51 mmol) in acetic anhydride (2 ml). The reaction was allowed to stir for 16 h until completion. The solvent was removed and the product partitioned between H_2O (3ml) and CH_2Cl_2 (3 ml). The organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation. The crude product was purified by column chromatography (2:1 Et_2O:Petroleum ether). 89 mg (73% yield) of a white crystalline solid were isolated, mp = 153-154°C.

^{1}H-NMR ($CDCl_3$ 400MHz): δ = 1.74-1.86 (m, 3H, Ar-CH_2-C*H*H-CH_2), 1.91 (s, 3H, CH_3), 2.14-2.23 (m, 1H, CH_2-C*H*H-CH_2), 2.71-2.95 (m, 2H, CH_2-Ar), 6.54 (s, 1H, C*H*-OAc), 7.12 (d, J = 5.6 Hz, 1H, Ar), 7.33 (t, J = 7.2 Hz, 1H, Ar), 7.41 (t, J = 7.4 Hz, 1H, Ar), 7.61 (d, J = 16.7 Hz, 1H, Ar), 7.69 (t, J = 8.3 Hz, 2H, Ar); ^{13}C-NMR ($CDCl_3$ 400 MHz): δ = 18.1 (CH_2-*C*H_2-CH_2), 21.8 (*C*H_2-CHOAc), 29.6 (*C*H_2-Ar), 30.5 (*C*H-OAc), 66.6 (CH_3-C=O), 122.3 (*C*H, Ar), 125.6 (*C*H, Ar), 127.2 (*C*H, Ar), 128.2 (*C*H, Ar), 128.4 (*C*H, Ar), 129.0 (*C*H, Ar), 129.3 (*C*, Ar), 132.7 (*C*, Ar), 132.8 (*C*, Ar), 137.2 (*C*, Ar), 171.2 (*C*=O) ppm; IR (KBr): 3446.0, 2930.1, 2362.3, 1724.2, 1369.1, 1235.2, 1062.3, 944.3, 811.3, 688.2; MS (EI) *m/z* (%): 240 (23) [M^+], 198 (14), 180 (100), 164 (60), 152 (30), 140 (72), 115 (35) 90 (29), 76 (18); HRMS: calcd. for $C_{16}H_{16}O_2$+NH_4^+ 258,1489, found 258.1487.

Enzymatic Resolution of 1,2,3,4-Tetrahydrophenanthren-4-ol 73:

Racemic 1,2,3,4-Tetrahydrophenanthren-4-ol **73** (500 mg, 32 mmol) was dissolved in toluene (5 mL) and vinylacetate (1 mL) and cross-linked enzyme crystals (PC-CLEC) (5 mg) were added. The mixture was shaken for 22 h at room temperature and the reaction monitored by HPLC. The mixture was filtrated, the solvent removed in vacuo, and the residue purified by flash chromatography on silica gel (Et_2O:pentane 1:2). Yields: (S)-1,2,3,4-Tetrahydrophenanthren-4-ol: 255 mg (45%), (R)-1,2,3,4-Tetrahydro-phenanthrenyl-4-acetate 74: 155 mg (22%) after recrystallization from Et_2O. Enantiomerically pure as determined by HPLC (Chiracel OD, 25°C, *n*-hexane/2-propanol 90:10, 254 nm, 0.5 $mLmin^{-1}$, Rf(*S*) 8.3 min, Rf(*R*) 9.7 min.

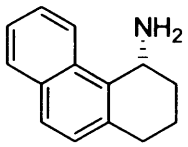
4-Azido-1,2,3,4-tetrahydrophenanthrene 75:



Mesyl chloride (50 µl, 0.404 mmol) was added to a solution of 1,2,3,4-tetrahydrophenanthren-4-ol (20 mg, 0.101 mmol), DMAP (74 mg, 0.606 mmol) and NaN_3 (328 mg, 5.05 mmol) in CH_2Cl_2 (3 mL) at 0°C. After 30 min the reaction mixture was allowed to warm to rt and DMSO (1.5 mL) was added. The mixture was stirrd for 3 d and then quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL) and the combined organic layers were washed with sat. aq. NaCl (4 x 5 mL) and dried over $MgSO_4$. The solvent was evaporated dried over $MgSO_4$, the solvent was evaporated, and the crude product was purified by flash chromatography on silica gel using diethyl ether/petroleum ether (2:1) as eluent to yield 17 mg (75%) of product. The racemate was separated by preparative HPLC (Chiracel OD 20 mm x 250 mm, 5 ml/min, 15 °C), $R_f(R)$ = 10.1 min, $[\alpha]^{20}_D$ = +278 (c = 0.35, $CHCl_3$); $R_f(S)$ = 18.8 min, $[\alpha]^{20}_D$ = –276 (c = 0.35, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.82-2.05 (m, 3H, CH_2-C*H*H-C*H*$_2$), 2.22-2.38 (m, 1H, CH_2-C*H*H-CH_2), 2.77-2.98 (m, 2H, CH_2-Ar), 5.04 (s, 1H, C*H*-N_3, one would expect a triplet, but even in the expansion no splitting is visible) , 7.14 (d, J = 8.1 Hz, 1H, Ar), 7.39 (dt, J = 5.6 Hz, J = 1.3 Hz, 1H, Ar), 7.48 (dt, J = 7.1 Hz, J = 0.6 Hz, 1H, Ar), 7.66 (d, J = 8.5 Hz, 1H, Ar), 7.73 (d, J = 7.5 Hz, 1H, Ar), 8.0 (d, J = 8.9 Hz, 1H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.9 (CH_2-*C*H_2-CH_2), 28.6 (*C*H_2-CHN_3), 28.8 (*C*H_2-Ar), 53.9 (*C*H-N_3), 121.7 (*C*H, Ar), 124.3 (*C*H, Ar), 125.8 (*C*H, Ar), 126.1 (*C*H, Ar), 126.7 (*C*H, Ar), 127.6 (*C*H, Ar), 127.8 (*C*, Ar), 131.1 (*C*, Ar), 131.4 (*C*, Ar), 135.1 (*C*, Ar) ppm; IR (thin film): ν = 3051, 2938, 2094, 1626, 1602, 1510, 1430, 1292, 1263, 1233, 1190, 1058, 901, 848, 814, 743 cm^{-1}; MS (EI) *m/z* (%): 223 (12) $[M]^+$, 194 (9), 181 (100), 165 (28), 149 (15), 139 (18), 97(22), 83 (34), 69 (35), 57 (38), 40 (54); HMRS calcd for $C_{14}H_{13}N_3$: 223.1104, found 223.1101

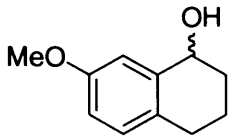
(*R*)-1,2,3,4-Tetrahydrophenanthrene-4-amine 76:



(*R*)-4-Azido-1,2,3,4-tetrahydrophenanthrene **75** (86 mg, 0.39 mmol) was dissolved in anhydrous methanol and 10% palladium on charcoal (2 mg) was added. The solvent was then thoroughly degassed and then saturated with H_2. The reaction mixture was allowed to stir for 30 min. No trace of starting material was observed by TLC. The solution was filtered through celite and the solvent removed under reduced pressure. Purification by preparative TLC (ethyl acetate:MeOH 4:1) yielded 20 mg (26%) of product. Spectroscopic data identical to that previously reported for the racemic material.

(*R*) $[\alpha]^{20}_D$ = +22 (c = 1, $CHCl_3$); (*S*)$[\alpha]^{20}_D$ = –22 (c = 1, $CHCl_3$).

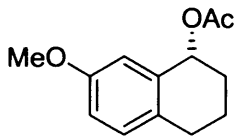
1-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphtalene 77:[46]



$NaBH_4$ (15 mg, 0.39 mmol) was added to a solution of 7-methoxy-1-tetralone (501 mg, 0.35 mmol) in MeOH cooled to 0 °C. The reaction mixture was warmed to room temperature and allowed to react for 6 h. The solvent was removed by rotary evaporation and the solid product was partition between CH_2Cl_2 (3 ml) and sat. aqueous ammonium chloride (3 ml). The aqueous phase was extracted a further three times with CH_2Cl_2 (3 ml) and the combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporation to give 498 mg of a clear yellow oil (98% yield). For further spectroscopic data see reference.[46]

^{1}H-NMR ($CDCl_3$ 250MHz): δ = 1.7-2.10 (m, 4H, C*H*$_2$-C*H*$_2$-CHOH), 2.63-2.72 (m, 2H, CH_2-Ar), 3.75 (s, 3H, C*H*$_3$-OR), 4.68-4.71 (m, 1H, C*H*-OH), 6.74-6.77 (m, 1H, Ar), 6.96-7.0 (m, 2H, Ar) ppm.

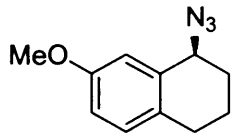
(*R*)-Acetic acid 7-methoxy-1,2,3,4-tetrahydro-1-naphthalene-1-yl ester 79:[46]



Prepared in 25 % yield from the enzymatic resolution of **77** (1 g, 5.6 mmol) according to the procedure of Wirth *et al.*[46] Enantiomerically pure as determined by HPLC (Chiracel OD, 25 °C, *n*-hexane/2-propanol 95:5, 254 nm, 0.5 mLmin^{-1}, Rf(*S*) 33.7 min, Rf(*R*) 38.2 min. For further spectroscopic data see reference.[46]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.75-1.98 (m, 4H, CH_2-CH_2-CHOAc), 2.08 (s, 3H, CH_3C=O), 2.63-2.83 (m, 2H, CH_2-Ar), 3.77 (s, 3H, CH_3-OR), 5.96 (t, J = 4.2 Hz, 1H, CH-OAc), 6.78-6.82 (m, 2H, Ar), 7.03 (d, J = 9.1 Hz, 1H, Ar) ppm.

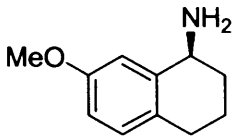
(*S*)-1-Azido-7-methoxy-1,2,3,4-tetrahydronaphthalene 80:



(*R*)-1-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene **77** (110 mg, 0.62 mmol) was dissolved in toluene (2.3 mL) and diphenylphosphorylazide (166 mg, 0.68 mmol) was added. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (160 mg, 1 mmol) was then added and the reaction was stirred overnight at room temperature. The reaction mixture was then partitioned between CH_2Cl_2 and saturated NH_4Cl, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting clear yellow oil was purified by performing flash chromatography (*t*-butylmethyl ether/pentane 1:9) to yield 86 mg (68%) of (*R*)-1-azido-7-methoxy-1,2,3,4-tetrahydronaphthalene.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.62–1.93 (m, 4H, CH_2-CH_2-CHOH), 2.49–2.73 (m, 2H, CH_2-Ar), 3.72 (s, 3H, CH_3-OR), 4.66 (t, J = 6.3 Hz, 1H, CH-N_3), 6.58–6.74 (m, 2H, Ar), 6.89–7.02 (m, 1H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 19.4 (CH_2-CH_2-CH_2), 28.0 (CH_2-CHN_3), 29.2 (CH_2-Ar), 55.4 (CH-N_3), 59.7 (CH_3-OR), 113.3 (*C*H, Ar), 114.8 (*C*H, Ar), 129.4 (*C*H, Ar), 130.4 (*C*, Ar), 134.7 (*C*, Ar), 157.8 (*C*-OR) ppm; IR (neat): ν = 2932, 2835, 2361, 2341, 2096, 1614, 1505, 1456, 1254, 1149, 1039, 808, 668 cm^{-1}; MS (EI): m/z (%): 203 (10) [M+], 174 (9), 161 (100), 146 (12), 128 (8), 115 (15), 89 (9), 74 (7), 51 (16); HRMS: calcd for $C_{11}H_{14}N_3$ $[M+H]^+$: 204.2511; found: 204.2513.

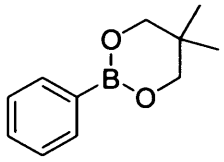
(*S*)-7-Methoxy-1,2,3,4-tetrahydronaphthylamine 50:[113]



1-Azido-7-methoxy-1,2,3,4-tetrahydronaphthalene (86 mg, 0.39 mmol) was dissolved in anhydrous methanol, and 10% palladium on charcoal (2 mg) was added. The solvent was then thoroughly degassed and saturated with H_2. The reaction mixture was stirred for 30 min. The resulting brown oil was purified by preparative TLC (ethyl acetate/MeOH 4:1) yielded 20 mg (30%) of product. For further spectroscopic data see reference.[113]

^{1}H NMR ($CDCl_3$ 250 MHz): δ= 1.78–2.01 (m, 4 H), 2.68–2.78 (m, 2 H), 3.90 (s,3H), 3.95 (t, J = 6 Hz, 1H), 6.76 (m, 1H), 7.00 (m, 2H) ppm; ^{13}C NMR: δ= 19.5 (CH_2-*C*H_2-CH_2), 28.4 (*C*H_2-$CHNH_2$), 31.8 (*C*H_2-Ar), 49.7 (*C*H-NH_2), 55.4 (*C*H_3-OR), 112.3 (*C*H, Ar), 114.2 (*C*H, Ar), 127.4 (*C*, Ar) 129.3 (*C*, Ar), 130.1 (*C*, Ar), 157.9 (*C*-OCH_3) ppm.

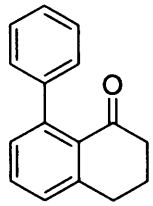
5,5-Dimethyl-2-phenyl-1,3,2-dioxaborinane 82:[48]



Prepared by via the condensation of phenyl boronic acid (3g, 15.7 mmol) with neopentyl glycol according to the procedure of Kakiuchi *et al.*[48] The product was isolated in 96% yield as a colourless crystalline material, mp = 61-63°C. For further spectroscopic data see reference.[48]

^{1}H NMR($CDCl_3$ 400 MHz): δ= 0.89 (s, 6H, 2(CH_3)), 3.65 (s, 4H, 2(CH_2)), 7.24 (td, J = 6.3, 1.0 Hz, 2H, Ar), 7.32 (m, 1H, Ar), 7.76 (dd, J = 8.0, 1.0 Hz, 2H, Ar) ppm.

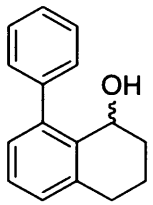
8-Phenyl-3,4-dihydro-2*H*-naphthalen-1-one 81:[48]



Prepared by treatment of tetralone (500mg, 3.4 mmol) with **73** in the presence of a ruthenium catalyst, according to the procedure of Kakiuchi *et al.*[48] The product was isolated in 67% yield as a red crystalline material, mp = 63-65°C. For further spectroscopic data see reference.[48]

^{1}H NMR ($CDCl_3$ 400 MHz): δ = 2.13 (tt, J = 6.5, 5.9 Hz, 2H, CH_2-CH_2-CH_2), 2.61 (t, J = 6.5 Hz, 2H, CH_2-C=O), 3.00 (t, J =5.9 Hz, 2H, Ar-CH_2), 7.08-7.46 (m, 8H, Ar-*H*).

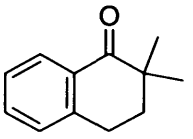
1,2,3,4-Tetrahydro-8-phenylnaphthalen-1-ol 85:



$NaBH_4$ (57 mg, 1.5 mmol) was added to a solution of 8-Phenyl-3,4-dihydro-2*H*-naphthalen-1-one **81** (300 mg, 1.36 mmol) in MeOH at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h. The solvent was evaporated and the residue treated with sat. aq. NH_4Cl (3 mL) and extracted with CH_2Cl_2 (4 x 3 mL). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated to yield 301 mg (98%) of a colourless crystalline product mp = 166-168°C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.62–1.71 (m, 2H, CH_2-CH_2-CHOH), 1.88-1.99 (m, 2H, CH_2-CHOH), 2.72 (ddd, J = 16.9, 11.7, 5.8 Hz, 1H, C*H*H-Ar), 2.86 (dt, J = 17.8, 4.3 Hz, 1H, C*H*H-Ar), 4.77 (t, J = 3.6 Hz, 1H, C*H*-OH), 6.97 (d, J = 7.4, 1H, Ar), 7.10 (d, J = 7.5, 1H, Ar), 7.20 (t, J = 7.6, 1H, Ar), 7.27–7.35 (m, 6H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 17.3 (CH_2-*C*H_2-CH_2), 30.9 (*C*H_2-CHOH), 31.1 (*C*H_2-Ar), 64.0 (*C*H-OH), 127.7 (*C*H, Ar), 127.8 (*C*H, Ar), 128.0 (*C*H, Ar), 128.3 (*C*H, Ar), 128.5 (*C*H, Ar), 129.3 (*C*H, Ar), 137.5 (*C*, Ar), 139.0 (*C*, Ar), 141.2 (*C*, Ar), 143.0 (*C*, Ar) ppm; IR (neat): ν = 3392, 2936, 2245, 1586, 1463, 1070, 962, 910, 762, 703 cm^{-1}; MS (EI) *m/z* (%): 224 (34) [M$^+$], 206 (89), 196 (100), 192 (26), 181 (30), 176 (34), 114 (35) 90 (29), 76 (18); HRMS: calcd for $C_{16}H_{16}O$ [M+H]$^+$: 242.1545; found: 242.1547.

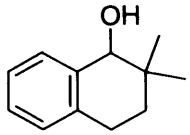
2,2-Dimethyl-3,4-dihydro-2*H*-naphthalen-1-one 87:[49]



Prepared by treatment of tetralone (1g, 6.8 mmol) with NaH in the presence of methyl iodide, according to the procedure of Coogan *et al.*[49] The product was isolated as a clear yellow oil in 73% yield. For further spectroscopic data see reference.[49]

^{1}H NMR ($CDCl_3$ 400 MHz): δ = 1.14 (s, 6H, 2(CH_3)), 1.98 (t, J = 6.3 Hz, 2H, CH_2-C(CH_3)$_2$), 2.98 (t, J = 6.3 Hz, 2H, CH_2-Ar), 7.22 (d, J=7.6 Hz, 1H, Ar), 7.30 (dd, J = 7.6, 7.6 Hz, 1H, Ar), 7.45 (dd, J = 7.6, 7.6 Hz, 1H, Ar), 8.05 (d, J = 7.6 Hz, 1H, Ar) ppm.

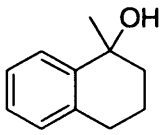
1,2,3,4-Tetrahydro-2,2-dimethylnaphthalen-1-ol 88:[114]



Prepared by reduction of **87** (500 mg, 2.8 mmol) with sodium borohydride , according to the procedure of Coogan *et al.*[49] The product was isolated as a clear yellow oil in 89% yield. For further spectroscopic data see literature.[114]

^{1}H NMR ($CDCl_3$ 400 MHz): δ = 0.98 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.47-1.85 (m, 2H, CH_2-C(CH_3)), 2.75-2.83 (m, 2H, CH_2-Ar), 4.25 (d, J = 6.9 Hz, 1H, C*H*-OH), 7.07–7.12 (m, 1H, Ar), 7.16–7.22 (m, 2H, Ar), 7.41–7.45 (m, 1H, Ar) ppm.

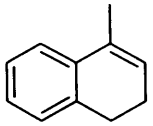
1,2,3,4-Tetrahydro-1-methylnaphthalen-1-ol 90:[115]



Synthesised from tetralone (1g, 6.8 mmol) via the addition of methyl Grignard according to the procedure of Noji *et al.* [115] The product was isolated in 69% yield as a colourless crystalline material, mp = 86-88°C. For further spectroscopic data see reference.[115]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (s, 3H, CH_3), 1.76-1.97 (m, 4H, ArCH2 *CH*2*CH*2), 2.70-2.88 (m, 2H, CH_2-Ar), 7.04-7.09 (m, 1H, Ar), 7.24.7.13 (m, 2H, Ar), 7.58 (dd, J = 7.5, 1.5 Hz, 1H, Ar) ppm.

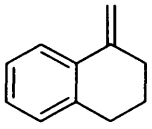
1,2-Dihydro-4-methylnaphthalene 91:[116]



Isolated as a by-product from reactions of **90** and **92**. For further spectroscopic data see reference.[116]

^{1}H NMR ($CDCl_3$ 400 MHz): δ = 2.02 (s, 3H, CH_3), 2.12-2.32 (m, 2H, C*H*$_2$-CH=C), 2.7-2.80 (m, 2H, CH_2-Ar), 5.80-5.88 (m, 1H, C*H*=C), 7.04-7.28 (m, 4, Ar) ppm.

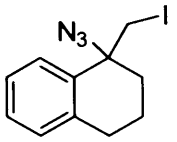
1,2,3,4-Tetrahydro-1-methylenenaphthalene 92:[117]



Synthesised in 63% yield from tetralone (1g, 6.8 mmol) according to the procedure of Campbelle *et al.*[51] The product was isolated in 63% yield as a colourless oil. For further spectroscopic data see reference.[117]

^{1}H NMR ($CDCl_3$ 400 MHz) δ = 1.90 (m, 2H, CH_2-C*H*$_2$-CH_2), 2.51 (t, J = 6.5 Hz, 2H, C*H*$_2$-C=CH_2), 2.80 (t, J = 6.4 Hz, 2H, C*H*$_2$-Ar), 4.95 (s, 1H, C=C*H*H), 5.45 (s, 1H,C=C*H*H), 7.01-7.62 (m, 4H, Ar).

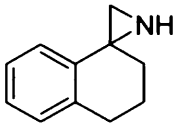
1-Azido-1,2,3,4-tetrahydro-1-(iodomethyl)naphthalene 93:[51]



Synthesised in by addition of ICl and NaN_3 to **92** (500mg, 3.5 mmol) according to the procedure of Campbelle *et al*.[51] The product was isolated as a clear yellow oil in 73% yield. For further spectroscopic data see reference.[51]

^{1}H NMR ($CDCl_3$ 400 MHz) δ= 1.62-2.41 (m, 4H, Ar-CH2-C*H*$_2$-C*H*$_2$), 2.79 (t, J = 4.1 Hz, 2H, C*H*$_2$-Ar), 3.45(s, 2H, C*H*$_2$I), 7.20-7.52 (m, 4H, Ar) ppm.

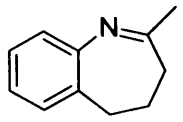
1,2,3,4-Tetrahydronaphthalen-1,2'-(1*H*-azacyclopropane) 94:[51]



Prepared from the reduction of **93** (250 mg, 0.8 mmol) according to the procedure of Campbelle *et al.*[51] The product was isolated as a clear yellow oil in 55% yield. For further spectroscopic data see reference.[51]

^{1}H NMR ($CDCl_3$ 400 MHz) δ= 1.76-2.05 (m, 6H, Ar-C*H*$_2$-C*H*$_2$-C*H*$_2$), 2.90 (t, J = 4.3 Hz, C*H*$_2$-NH), 6.60-7.25 (m, 4H, Ar) ppm.

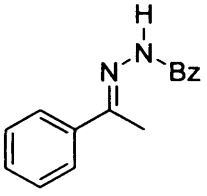
(Z)-4,5-Dihydro-2-methyl-3H-benzo[b]azepine 96:[54]



The clear yellow oil as isolated in 79% yield as the major product from the reaction of **92** (250 mg, 1.7 mmol) with HN_3 according to the procedure of Andrieux *et al.*[54] For further spectroscopic data see reference.[54]

^{1}H NMR ($CDCl_3$ 400 MHz): δ = 1.65 (s, 3H, CH_3), 1.73 (t, J = 7.6 Hz, 2H, CH_2-), 1.95 (m, 2H, CH_2-CH_2-CH_2), 2.80 (t, J = 7.6 Hz, 2H, CH_2-Ar), 7.00 -7.75 (m, 4H, Ar) ppm.

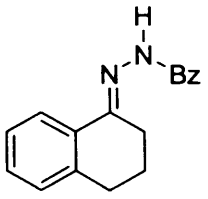
(*E*)-*N*'-(1-Phenylethylidene)benzohydrazide 98:[118]



Synthesised via the condensation of acetophenone (3g, 25 mmol) with benzoylhydrazine according to the procedure of Leighton *et al.*[56] The product was isolated in 89% yield as a colourless crystalline material, mp = 153-155°C. For further spectroscopic data see reference.[118]

^{1}H NMR ($CDCl_3$ 250 MHz): δ = 2.32 (s, 3H, CH_3), 7.30-8.0 (m, 10H, Ar) ppm.

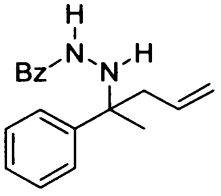
(*E*)-*N*'-(2,3-Dihydronaphthalen-4(1*H*)-ylidene)benzohydrazide 99:[119]



Synthesised via the condensation of tetralone (3g, 20 mmol) with benzoylhydrazine according to the procedure of Leighton *et al.*[56] The product was isolated in 76% yield as a colourless crystalline material, mp = 158-160°C For further spectroscopic data see reference.[119]

^{1}H NMR ($CDCl_3$ 400 MHz) δ= 1.65-2.43 (m, 4H, Ar-CH2-CH_2-CH_2), 2.71 (t, J = 4,1 Hz, CH_2-Ar), 7.30-8.0 (m, 10H, Ar) ppm.

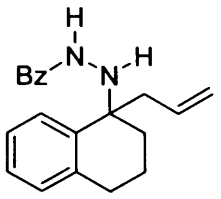
***N*'-(2-Phenylpent-4-en-2-yl)benzohydrazide 102:**[56]



Synthesised from the reaction of **98** (200mg, 0.8 mmol) with allyl trichlorsilane in DMF according to the procedure of Hirabayashi *et al.* [57] The product was isolated in 89% yield as a colourless oil. For further spectroscopic data see reference.[57]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (s, 3H, CH_3), 2.52 (dd, J = 13.7, 8.0 Hz, 1H, C*H*H-CH=CH_2), 2.62 (dd, J = 13.7, 6.6 Hz, 1H, C*H*H-CH=CH_2), 5.07-5.12 (m, 2H, CH_2CH=CH_2), 5.63-5.72 (m, 1H, CH_2C*H*=CH_2), 7.29 (t, J = 7.3 Hz, 1H, Ar), 7.36-7.41 (m, 4H, Ar), 7.47 (t, J = 7.3 Hz, 1H, Ar), 7.54-7.60 (m, 4H, Ar) ppm.

***N'*-(1-Allyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzohydrazide 103:**[56]



Synthesised from the reaction of **99** (200mg, 0.75 mmol) with allyl trichlorsilane in DMF according to the procedure of Hirabayashi *et al.* [57] The product was isolated in 67% yield as a colourless oil. For further spectroscopic data see reference.[56]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67-2.45 (m, 4H, Ar-CH2-CH_2-CH_2), 2.74 (t, J = 4,4 1 Hz, CH_2-Ar), 2.49 (dd, J = 13.5, 8.1 Hz, 1H, CHH-CH=CH_2), 2.62 (dd, J = 13.8, 6.4 Hz, 1H, CHH-CH=CH_2), 5.08-5.13 (m, 2H, CH_2CH=CH_2), 5.64-5.73 (m, 1H, CH_2CH=CH_2), 7.31 (t, J = 7.3 Hz, 1H, Ar), 7.35-7.42 (m, 4H, Ar), 7.48 (t, J = 7.2 Hz, 1H, Ar), 7.51-7.59 (m, 4H, Ar) ppm.

Enantoselective allylation of benzylhydrazones 98 and 99

A modified procedure to that developed by Leighton *et al* was employed.[56] Triethylamine (0.43 ml, 3 mmol) was added to a solution of pseudoephedrine (250 mg, 1.5 mmol) dissolved in CH_2Cl_2 (4 ml). Allyltrichlorosilane (0.250 ml, 1.75 mmol) was then added dropwise and the mixture was allowed to stir for 16 hours. The resulting slurry was filtered under argon and the filtrate was washed with CH_2Cl_2 (2 x 2 ml). The resulting reagent was used without further purification. The solution of **100** was assumed to be 0.18 M.

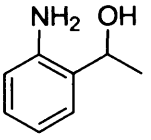
4 ml of a 0.18 M solution of **100** (0.75 mmol) in CH_2Cl_2 were added to a solution of the benzoylhydrazone (0.5 mmol) in CH_2Cl_2 (3 mL) and the resulting mixture was stirred at 40°C for 24 h. The reaction was quenched with methanol (1.5 mL), stirred for 15 min, and then concentrated. The residue was diluted with EtOAc (2 mL) and H_2O (5 mL) was added, the phases were separated, and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with

brine (1 x 5 mL), dried over $MgSO_4$ and concentrated by rotary evaporation. Purification by flash chromatography on silica gel yielded the pure hydrazide products. Yields and *ee*:

102, recovered in 32% yield, 53% *ee* as determined by HPLC (Chiracel OD 20 mm x 250 mm, 5 $mlmin^{-1}$, 15 °C, n-hexane:2-propanol 90:10), R_f1 = 13.2 min, R_f2 = 17.7 min.

103, recovered in 29% yield, 52% *ee* as determined by HPLC (Chiracel OD 20 mm x 250 mm, 5 $mlmin^{-1}$, 15 °C, n-hexane:2-propanol 90:10), R_f1 = 10.2 min, R_f2 = 18.9 min.

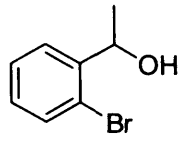
1-(2-Aminophenyl)ethanol 57:[120]



Synthesised by the reduction of amino acetophenone with sodium borohydride according to the procedure of Fleming *et al.*[120] The product was isolated in 94% yield as a colourless oil. For further spectroscopic data see reference.[120]

1H NMR (400 MHz, $CDCl_3$) 1.54 (d, 3H, J = 6.6, CH_3), 4.87 (q, 1H, J = 6.6, C*H*-OH), 6.59-6.68 (m, 2H, Ar-*H*), 6.99-7.10 (m, 2H, Ar).

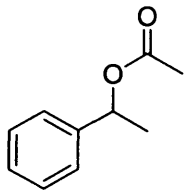
1-(2-Bromo phenyl)-ethanol 106:[121]



Synhesised by reduction of 2-bromoacetophenone (1g, 4.1 mmol) with sodium borohydride. The product was obtained in 97% yield as a colourless viscous oil. For further spectroscopic data see literature.[121]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.41 (d, J = 6.8 Hz, 3H), 5.18 (q, J = 6.4 Hz, 1H), 7.05 (dt, J = 1.6, 7.6 Hz, 1H), 7. 27 (dt, J = 0.8, 7.6 Hz, 1H), 7.44 (dd, J = 1.2, 8.0 Hz, 1H) 7.52 (dd, J = 1 .6, 8.0 Hz 1H) ppm.

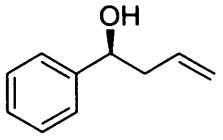
1-Phenylethyl acetate 110:[122]



Synhesised by treatment of 1-phenylethanol (500mg, 8.2 mmol) with acetyl chloride according to the procedure of Chandrasekhar *et al.*[122] The product was obtained in 86% yield as a clear oil. For further spectroscopic data see literature.[122]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.53 (d, J = 6.6 Hz, 3H, CH_3-CHO), 2.07 (s, 3H, CH_3-C=O), 5.86 (q, J = 6.9 Hz, 1H, CH-OAc), 7.27-7.36 (m, 5H, Ar) ppm.

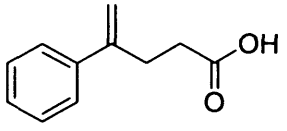
(*S*)-1-Phenylbut-3-en-1-ol 115:[123]



Prepared from benzaldehyde (20mg, 0.18 mmol) by treatment with allyl TADDOL titanium complex **112** according to the procedure of Duthaler *et al.*[63] The product was isolated in 88% yield, 95% *ee*. Enantiomeric excess was determined by HPLC (Chiracel OD 20 mm x 250 mm, 5 ml/min, 15 °C *n*-hexane:2-propanol, 95:5), $R_f(R)$ = 10.1 min, $R_f(S)$ = 12.8 min. For further spectroscopic data see literature.[123]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.29-2.48 (m, 2H, C*H*$_2$), 4.59-4.78 (m, lH, C*H*H=CH-CH$_2$), 5.10-5.19 (m, 1H, C*H*H=CH-CH$_2$), 5.72-5.91 (m, lH, CH$_2$=C*H*-CH$_2$), 7.26-7.39 (m. 5H, Ar) ppm.

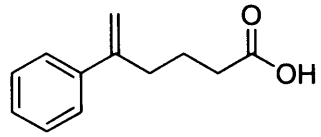
4-Phenylpent-4-enoic acid 118:[64]



Prepared from 4-oxo-4-phenylbutanoic acid **120** (1.5g, 8.4 mmol) via a Wittig reaction according to the procedure of Handa *et al.*[64] The product was isolated in 67% yield as a colourless crystalline material, mp = 96-98°C For further spectroscopic data see reference.[64]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.45 (t, J = 6.5 Hz, 2H, C*H*$_2$-C=CH$_2$), 2.78 (t, J = 6.7 Hz, 2H, C*H*$_2$-COOH), 4.98 (d, J = 1 Hz, 1H, C*H*H=C), 5.18 (d, J = 1 Hz, 1H, C*H*H=C), 7.12-7.34 (m, 5H, Ar) ppm.

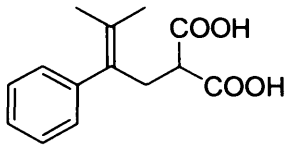
5-Phenylhex-5-enoic acid 122:



n-Buli (6.72 ml, 2.5 M in *n*-hexane, 14 mmol) was added dropwise to a solution of 5-oxo-5-phenylpentanoic acid **121** (2.5 g, 13 mmol) dissolved a 1:1 mixture of THF:DMSO (20 ml). The reaction mixture was then heated to reflux for 30 min. In a separate flack, *n*-Buli (6.72 ml, 2.5 M in *n*-hexane, 14 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (5.58 g, 14 mmol) in THF:DMSO (1:1. 15 ml). The reaction mixture was allowed to stir for 30 min. at room temperature. The deprotonated acid was then added by means of a cannula and the mixture was heated to 65 °C for 2 h. The reaction was then quenched by addition of MeOH (5 ml), filtered, and the solvent removed at reduced pressure. The resulting crude product was purified by recrystalisation (DCM : petrol ether). 1.65 g (67% yield) of a colourless crystalline solid was obtained, mp = 116-118 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.63-1.72 (m, 2H, CH_2-C*H*$_2$-CH_2), 2.27 (t, J = 7.4 Hz, 2H, C*H*$_2$-C=CH_2), 2.49 (t, J = 7.4 Hz, 2H, C*H*$_2$-COOH), 4.99 (d, J = 1 Hz, 1H, C*H*H=C), 5.23 (d, J = 1 Hz, 1H, C*H*H=C), 7.13-7.31 (m, 5H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.0 (CH_2-*C*H$_2$-CH_2), 33.4 (*C*H$_2$-C=CH_2), 34.5 (C*H*$_2$-COOH), 133.2 (*C*=CH_2), 125.7 (*C*, Ar), 127.6 (*C*, Ar), 128.4 (*C*, Ar), 140.7 (*C*=CH_2), 147.3 (*C*, Ar), 180.3 (*C*OOH) ppm; IR (KBr): ν = 2955, 2360, 1713, 1420, 1249, 1199, 888, 118, 704 cm^{-1}; MS (EI): m/z (%): 190 (25) [M+], 172 (38), 161 (100), 146 (12), 128 (8), 115 (15), 89 (14), 51 (18); HRMS: calcd for $C_{12}H_{14}O_2$ $[M+H]^+$: 208.1338; found: 208.1341.

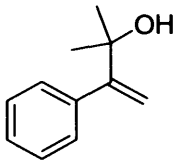
2-(3-Methyl-2-phenylbut-2-enyl)malonic acid 126:[66]



Synthesised from α-isopropylstyrene according to the procedure of Zimmerman *et al.*[66] The product was isolated in 53% yield as a pale yellow crystalline material, mp = 145-146°C For further spectroscopic data see reference.[66]

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.47 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.46 (d, J = 7.5 Hz, 2H, CH_2), 4.9 (t, J = 7.3 Hz, 1H, CH-CH_2), 7.34-7.61 (m, 5 H) ppm.

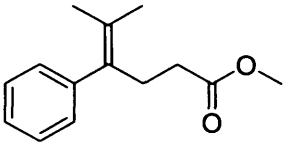
2-Methyl-3-phenylbut-3-en-2-ol 128:[67]



Synthesised via the addition of the Grignard of α-bromostyrene (500mg, 2.7) with acetone according to the procedure of Foote *et al.*[67] The product was obtained in 89% yield as a pale yellow oil. For further spectroscopic data see reference.[67]

^{1}H NMR (CDCl3, 400 MHz): δ= 1.60 (s, 3H, CH), 1.68 (s, 3 H), 2.01 (s, 1 H), 4.90 (m, 1 H), 5.23 (s, 1 H), 7.21-7.52 (m, 5 H) ppm.

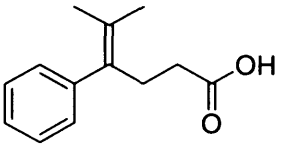
Methyl 5-methyl-4-phenylhex-4-enoate 130:



2-Methyl-3-phenylbut-3-en-2-ol (799 mg, 4.9 mmol), trimethyl orthoformate (5.88 g, 49 mmol), and acetic acid (30 mg, 0.5 mmol) were heated to 125 °C for 2 h. The temperature was increased to 140 °C for a further 6 h and the reaction mixture was then concentrated under reduced pressure. After recrystallization ($CHCl_3$:Hexane, 5:1), 431 mg methyl 5-methyl-4-phenylhex-4-enoate were obtained (40% yield), mp = 99-101°C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 1.45 (s, 3 H, CH_3), 1.72 (s, 3H, CH_3), 2.18 (t, J = 7.8 Hz, 2H, CH_2-COOCH$_3$), 2.61 (t, J = 7.8 Hz, 2 H, CH_2-C=), 3.53 (s, 3 H, CH_3-COOR), 6.98 (m, 2H, Ar), 7.12 (m, 1H, Ar), 7.20 ppm (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 20.5 (*C*H$_3$), 22.6 (*C*H$_3$), 30.0 (*C*H$_2$-C=), 33.2 (*C*H$_2$-COOH), 51.8 (*C*H$_2$-COOR), 126.5 ((CH$_3$)$_2$*C*=C), 128.3 (*C*H, Ar), 128.4 (*C*H, Ar), 129.0 (*C*H, Ar), 129.4 (Ar-*C*=C), 143.2 (*C*, Ar), 174.2 (*C*OOH) ppm.

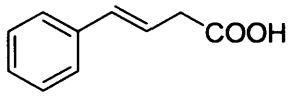
5-Methyl-4-phenylhex-4-enoic acid 123:



Methyl 5-methyl-4-phenylhex-4-enoate **130** (280 mg, 1.28 mmol) was dissolved in a 5:1 mixture of THF and water. LiOH (118 mg, 2.82 mmol) was added and the mixture was heated to reflux for 16 h. The reaction mixture was neutralized with 5n HCl and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed under reduced pressure, and the product purified by performing column chromatography (petroleum ether:Et_2O 4:1) to obtain **123** in 97% yield (257 mg) as a colourless oil.

^{1}H NMR (CDCl3, 400 MHz): δ= 1.43 (s, 3H, CH_3), 1.72 (s, 3 H, CH_3), 2.15 (t, J=7.8 Hz, 2H, CH_2-COOH), 2.61 (t, J=7.8 Hz, 2H, CH_2-C=), 6.98 (m, 2H, Ar), 7.12 (m, 1H, Ar), 7.20 ppm (m, 2H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ= 20.1 (CH_3), 22.3 (CH_3), 29.4 (CH_2-C=), 32.8 (CH_2-COOH), 126.2 ((CH_3)$_2$C=C), 128.1 (*C*H, Ar), 129.1 (*C*H, Ar), 129.2 (*C*H, Ar), 132.9 (Ar-C=C), 142.7 (*C*, Ar), 180.1 (COOH) ppm; IR (thin film): ν =3074, 2909, 2360, 1709, 1490, 1441, 1295, 1214, 1122, 1072, 1026, 929, 768, 702 cm^{-1}; MS: m/z (%): 204 (92) [M+], 143 (68), 128 (100), 115 (71), 91 (45), 73 (32), 65 (28), 51 (37); HRMS: calcd for $C_{13}H_{16}O_2$ [M+]: 204.2682; found: 204.2687.

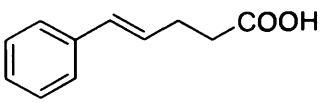
(*E*)-4-Phenylbut-3-enoic acid 131:[69]



Synthesised through the addition of malonic acid (3g, 29 mmol) to phenylacetaldehyde according to the procedure of Hoye *et al.*[69] The product was isolated in 78% yield as a colourless crystalline material, mp = 83-85°C. For further spectroscopic data see reference.[69]

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 3.10 (d, J = 6.4 Hz, 2H, CH_2), 6.04-6.13 (dt, J = 6.4, 16.0 Hz, 1H, *CH*-CH_2), 6.32 (d, J = 16.0 Hz, 1H, Ar-C*H*=C), 7.00-7.20 (m, 5H, Ar) ppm.

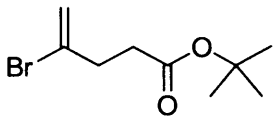
(*E*)-5-Phenylpent-4-enoic acid 132:[70]



Synthesised through the addition of malonic acid (3g, 29 mmol) to cinnamyl chloride according to the procedure of Hashem *et al.*[70] The product was isolated in 74% yield as a colourless crystalline material, mp = 91-92°C. For further spectroscopic data see reference.[70]

1H NMR ($CDCl_3$, 400 MHz): δ= 2.59-2.62 (m, 4H, CH_2), 6.24 (dt, J= 15, 6.5 Hz, 4H, *CH*-CH_2), 6.46 (d, J= 15Hz, 1H, Ar-CH=C). 7.22- 7.35 (m, 5H, Ar) ppm.

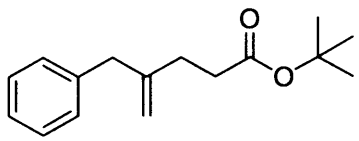
4-Bromo-pent-4-enoic acid tert-butyl ester 133:[71]



Synthesised from the reaction of tert-butyl acetate (2g, 17 mmol) with 2,3-dibromopropene in the presence of LDA, according to the procedure of Simoneau *et al.* The product was isolated as a colourless oil in 74% yield. For further spectroscopic data see reference.[71]

^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.48 (s, 9H, 3(C*H*$_3$)), 2.51 (t, J = 7.9, 2H, C*H*$_2$-C=O), 2.73 (t, J = 7.9, 2H, C*H*$_2$-C=C*H*$_2$), 5.42 (s, 1H, C*H*H=C), 5.64 (s, 1H, C*H*H=C) ppm.

***Tert*-butyl 4-benzylpent-4-enoate 137:**

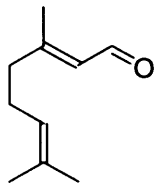


4-Bromo-pent-4-enoic acid tert-butyl ester **133** (100mg, 0,56 mmol) and 9-benzyl-9-BBN (2.24 ml, 0.5 M in THF, 0.56 mmol) were dissolved in DMF (5ml). $Pd(PPh_3)_4$ (19 mg, 0.3 mol%) and K_3PO_4 (118 g, 0.56 mmol) were added and the reaction

mixture was heated to 80 °C. After 16 h. all starting material was consumed (TLC). The mixture was allowed to cool to room temperature, was then filtered through celite and partitioned between water and petrol ether. The organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation. Purification by column chromatography afforded (petroleum ether/Et_2O 4:1) 68 mg (50% yield) of a colourless oil.

^1H NMR (400 MHz, $CDCl_3$): δ= 1.47 (s, 9H, 3(CH_3)), 2.31 (t, J = 7.9, 2H, CH_2-C=O), 2.43 (t, J = 7.2, 2H, CH_2-C=CH_2), 3.28 (s, 2H, CH_2-Ar), 4.75 (s, 1H, CH=C), 4.79 (s, 1H, CH=C), 7,06 (m, 5H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3 (CH_3), 31.0, 32.1 (CH2-COOH), 42.3 (CH_2-Ar), 87.4 ($C(CH_3)_3$), 101.8 (CH_2=C), 125.2 (CH, Ar), 127.6 (CH, Ar), 129.4 (CH, Ar), 138.2 (C=CH_2), 145.9 (C, Ar), 178.1 (COOH) ppm; IR (neat): ν = 2361, 1700, 1435, 1330, 1215, 942, 897, 792, 694 cm^{-1}; MS: m/z (%): 246 (45) [M+], 86 (100), 68 (53), 65 (28), 57 (37); HRMS: calcd for $C_{16}H_{22}O_2$ [M+]: 264.1964; found: 264.1967.

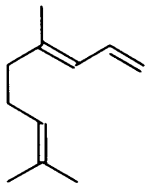
(*E*)-3,7-Dimethylocta-2,6-dienal (Geranial) 143:[75]



Synthesised via the Swern oxidation of geraniol (7g, 45 mmol) according to the procedure of Leopold.[75] The product was recovered as a pale yellow oil in 83% yield. For further spectroscopic data see reference.[75]

^1H NMR (400 MHz, $CDCl_3$): δ= 1.61 (s, 3H, CH_3-C-CH_3), 1.69 (s, 3H, CH_3-C-CH_3), 2.17 (s, 3H, CH_3), 2.19-2.23 (m, 4H, CH_2CH_2), 5.06 (s, 1H, (CH_3)-C=CH), 5.88 (d, J = 8 Hz, 1H, CH-CH=O), 9.99 (d, J = 8, 1H, CH=O) ppm

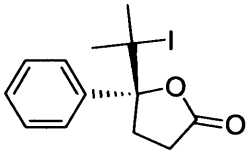
(*E*)-4,8-Dimethyl-1,3,7-nonatriene 144:[76]



Synthesised from the Wittig reaction of **143** (3g, 20 mmol) according to the procedure of Leopold.[75] The product was recovered as a pale yellow oil in 65% yield. For further spectroscopic data see reference.[75]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 3H, C*H*$_3$-C-CH$_3$), 1.68 (s, 3H, C*H*$_3$-C-CH$_3$), 1.76 (s, 3H, C*H*$_3$), 1.95-2.12 (m, 4H, C*H*$_2$C*H*$_2$), 4.80-5.15 (m, 3H, vinyl *H*), 5.85 (d, *J* = 10 Hz, C*H*-CH=CH$_2$), 6.55 (ddd, *J* = 8, 10, 17 Hz, 1H, CH-C*H*=CH$_2$) ppm.

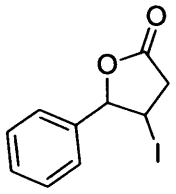
5-(2'-Iodo-2'methylethyl)-5-phenyldihydrofuran-2-one 154:



Synthesised from **123** (24mg, 0.115 mmol) using the standard iodolactonization procedure. Ms and melting point were not measured, due to sample decomposition. 45% *ee* as determined by HPLC (Chiracel OD 20 mm x 250 mm, 5 mlmin^{-1}, 15 °C, n-hexane:2-propanol 90:10), R_f1 = 14.2 min, R_f2 = 18.6 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.8 (s, 3H, C*H*$_3$), 2.03 (s, 3H, C*H*$_3$), 2.36–2.52 (m, 2H, C*H*$_2$-CH$_2$-C=O), 2.67–2.79 (m, 2H, CH$_2$-C*H*$_2$-C=O), 7.28–7.39 (m, 5H, Ar) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3 (*C*H$_3$), 20.8 (*C*H$_3$), 28.3 (*C*H$_2$-CH$_2$-C=O), 32.5 (*C*H$_2$-C=O), 41.6 (*C*-O), 83.2 (*C*-I), 123.8 (*C*H, Ar), 127.3 (*C*H, Ar), 129.3 (*C*H, Ar), 139.7 (*C*, Ar), 173.6 (C=O) ppm.

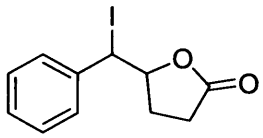
4-Iodo-5-phenyloxolan-2-one 155:[124]



Synthesised from **131** (19mg, 0.115 mmol) By cyclisation with ICl. For further spectroscopic data see reference.[124]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.92 (dd, J = 18.0, 9.6 Hz, 2H), 3.32 (dd, J = 18.0, 7.8 Hz, 1H), 4.27 (m, 1H), 5.67 (d, J =7.8 Hz, 5-H) ppm.

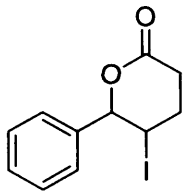
5-(Iodo-phenyl-methyl)-dihydrofuran-2-one 156:[81]



Synthesised from **132** (20mg, 0.115 mmol) using the standard iodolactonization procedure. For further spectroscopic data see reference.[81] 43% *ee* as determined by HPLC (Chiracel OD 20 mm x 250 mm, 5 mlmin^{-1}, 15 °C, n-hexane:2-propanol 90:10), R_f1 = 13.1 min, R_f2 = 16.2 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.12-2.20 (m, 1H, C*H*H-CH_2-C=O), 2.53-2.65 (m, 3H, C*H*H-C*H*$_2$-C=O), 4.86-4.92 (m, 1H, C*H*-O), 5.12 (d, J = 8.0 Hz, 1H, C*H*-Ar), 7.27-7.34 (m, 3H, Ar), 7.41 (d, J = 7.6 Hz, 2H, Ar) ppm.

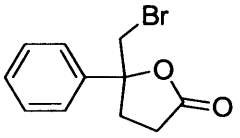
5-Iodo-6-phenyl-tetrahydro-pyran-2-one 157:[81]



Synthesised from **132** (20mg, 0.115 mmol) using the standard iodolactonization procedure. For further spectroscopic data see reference.[81] 42% *ee* as determined by HPLC (Chiracel OD 20 mm x 250 mm, 5 mlmin^{-1}, 15 °C, n-hexane:2-propanol 90:10), R_f1 = 15.1 min, R_f2 = 18.3 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.30-2.49 (m, 2H,), C*H*$_2$-CH$_2$-C=O 2.68-2.76 (m, 1H, CH$_2$-C*H*H-C=O), 2.82-2.90 (m, 1H, CH$_2$-C*H*H-C=O), 4.40-4.45 (m, 1H, C*H*-I), 5.60 (d, J = 8.0 Hz, 1H, C*H*-Ar), 7.32-7.34 (m,2H, Ar), 7.39-7.41 (m, 3H, Ar) ppm.

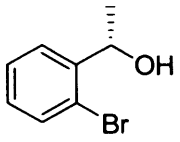
5-(Bromomethyl)-dihydro-5-phenylfuran-2-one 160:[125]



A mixture of NBS (23mg, 0.127 mmol) and diphenyldiselenide (1 mg, 3 mol%) dissolved MeCN (1 ml) was added to a solution of unsaturated carboxylic acid **118** (20 mg, 0.115 mmol) in MeCN (5ml) cooled to –40 °C. After 10 min, aqueous $Na_2S_2O_3$ (10%) was added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was extracted with CH_2Cl_2 (2x 6 mL) and the combined organic layers were dried with $MgSO_4$. The product was purified by preparative TLC (tert-butylmethyl ether/pentane 1:2). For further spectroscopic data see reference.[125] The racemate was resolved by HPLC (Chiracel OD 20 mm x 250 mm, 5 mlmin^{-1}, 15 °C, n-hexane:2-propanol 90:10), R_f1 = 16.4 min, R_f2 = 19.8 min.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.54 (m, 2H), 2.85 (m, 2H), 3.66 (d, J = 12.9 Hz, 1H), 3.72 (d, J = 12.9 Hz, 1H), 7.22-7.40 (m, 5H) ppm.

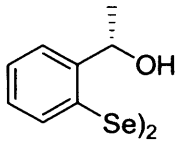
(*S*)-(-)-(2-Bromo phenyl)-ehtane-1-ol 161:[121]



Synthesised via the enantioselective reduction of 2-bromoacetophenone (1g, 50 mmol) according to the procedure of Wirth *et al.*[121] The colourless was purified by flash and isolated in 89 % yield, 96% *ee*. For further spectroscopic data see literature.[121]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.41 (d, J = 6.8 Hz, 3H), 5.18 (q, J = 6.4 Hz, 1H), 7.05 (dt, J = 1.6, 7.6 Hz, 1H), 7. 27 (dt, J = 0.8, 7.6 Hz, 1H), 7.44 (dd, J = 1.2, 8.0 Hz, 1H) 7.52 (dd, J = 1 .6, 8.0 Hz 1H) ppm.

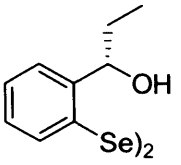
(*S*,*S*)-Bis –[2-(1-Hydroxyethyl)phenyl]-diselenide 162:[126]



Synthesised from (*S*)-(-)-(2-bromo phenyl)-ethane-1-ol **161** (500mg, 25 mmol) according to the procedure of Wirth *et al.*[126] The orange oil was purified by flash chromatography (petroleum ether:Et_2O 4:1). The product was obtained in 86% yield, 96% *ee*. For further spectroscopic data see reference.[126]

1H NMR ($CDCl_3$, 400 MHz): δ = 0.75 (t, J = 7.2 Hz, 3H), 1.53-1.63 (m, 2H), 4.68 (t, J = 6.8 Hz, 1H), 7.13 (dt, J = 1.2, 7.6Hz, 1H), 7.28 (dt, J = 1.2, 7.6 Hz, 1H), 7.38 (dd, J = 1.2, 7.6 Hz, 1H), 7.69 (dd, J = 1.2, 7.6 Hz 1H).

(*S*,*S*)-Bis –[2-(1-Hydroxypropyl)phenyl]-diselenide 165:[127]



Crude product obtained from Yan Gao of the Wirth Group. The orange oil was purified by flash chromatography (petroleum ether:Et_2O 4:1). The product was obtained in 85% yield, 97% *ee*. For further spectroscopic data see reference.[127]

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.82 (t, J = 7.0 Hz, 6H, CH_3), 1.65 (q, J = 7.0, 4H, CH_2), 4.76 (t, J = 7,3 Hz, 2H, C*H*-OH), 7.19 (t, J = 7,5 Hz, 2H, Ar), 7.33(t, J = 7,5 Hz, 2H, Ar), 7.45 (t, J = 7,5 Hz, 2H, Ar), 7.75 (t, J = 7,5 Hz, 2H, Ar) ppm.

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